BMJ Open

Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048338
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2020
Complete List of Authors:	Mathioudakis, Alexander; The University of Manchester, Division of Infection, Immunity and Respiratory Medicine; Manchester University NHS Foundation Trust, North West Lung Centre Miligkos, Michael ; University of Athens, First Department of Pediatrics, "Aghia Sofia" Children's Hospital, Boccabella, Cristina; Catholic University of the Sacred Heart, Department of Cardiovascular and Thoracic Sciences Alimani, Gioulinta; University of West Attica, Department of Biomedical Sciences; Athens Breath Centre, Pulmonology Custovic, Adnan; Imperial College London, Department of Paediatrics Deschildre, A.; CHU Lille, Unité de Pneumologie et Allergologie Pédiatriques, Hôpital Jeanne de Flandre, F-59000 Lille, France. Ducharme, Francine; University of Montreal, Pediatrics Kalayci, Omer; Hacettepe Universitesi, Pediatric Allergy and Asthma Unit Murray, Clare ; The University of Manchester, Division of Infection, Immunity and Respiratory Medicine, ; North West Lung Centre, Wythenshawe Hospital Garcia, Antonio; La Fe University and Polytechnic Hospital, Pulmonology and Allergy Unity Phipatanakul, Wanda; Children's Hospital Boston, Pediatric Allergy and Immunology Price, David; University of Aberdeen, Centre of Academic Primary Care Sheikh, Aziz; The University of Edinburgh, Division of Community Health Sciences Agache, Ioana; Transylvania University, Allergy and Clinical Immunology Bacharier, Leonard; University of Washington, Department of Immunology, and Pulmonary Medicine Beloukas, Apostolos; University of West Attica, Department of Biomedical Sciences; University of Liverpool Institute of Infection and Global Health, University of Liverpool Bentley, Andrew; University Hospital of South Manchester NHS Foundation Trust, Acute Intensive Care Unit; University Hospital of South Manchester NHS Foundation Trust, North West Lung Centre Bonini, Matteo; Catholic University of the Sacred Heart, Department of Cardiovascular and Thoracic Sciences; Imperial College London, Department of Cardiovascular and Thoracic Sciences Castro-Rodriguez, Jose A.; University of Chile, Department of Pediatrics De Carlo, Giuseppe; European Federation of Pharmaceutical Industries and Associations, Allergy and Airway Diseases Patient's Associations

	Craig, Timothy; Penn State, Asthma and Immunology Diamant, Z.; Skane University Hospital Lund Hematological Clinic, Department of Respiratory Medicine and Allergology, Institute for Clinical Science; Charles University, Department of Respiratory Medicine Prague Feleszko, Wojciech ; Medical University of Warsaw, Department of Pediatric Pulmonology and Allergy Felton, Tim; University of Manchester, Division of Infection, Immunity and Respiratory Medicine Gern, James; University of Wisconsin Colleges, Department of Pediatrics and Medicine Grigg, Jonathan; Queen Mary University of London, Paediatric Respiratory Hedlin, Gunilla; Karolinska Institute, Department of Women's and Childnren's Health Hossny, Elham M.; Ain Shams University, Pediatric Allergy and Immunology Unit Ierodiakonou, Despo; University of Crete, Department of Social Medicine Jartti, Tuomas; University of Turku, Department of Paediatrics Kaplan, Alan; Canada, Family Physician Lemanske, Robert F.; University of Wisconsin System, Department of Pediatrics and Medicine Le Souëf, Peter; University of Western Australia, Discipline of Paediatrics Mäkelä, Mika; University of Helsinki, Department of Allergy Mathioudakis, Georgios; Athens Breath Centre, Pulmonology Matricardi, Paolo; Charite Universitatsmedizin Berlin Mitrogiorgou, Marina; National and Kapodistrian University of Athens School of Health Sciences, Third Department of Paediatrics Morais-Almeida, Mario; Hospital CUF Descobertas, Allergy Center Nagaraju, Karthik; VN, Allergy & Asthma Papageorgiou, Effie; University of West Attica, Department of Biomedical Sciences Pité, H; Hospital CUF Descobertas, Allergy Center Pitrez, Paulo MC; Charite University Hospital Berlin, Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Pohunek, Petr; Motol University Hospital, Paediatric Department Roberts , Graham ; University of Southampton, Faculty of Medicine Tsiligianni, Ioanna; University of Crete Faculty of Medicine, Clinic of Social and Family Medicine Turner, Stephen; University of Aberdeen, Department of Child Health Susanne, Vijverberg; University of Amsterdam, Department of Respiratory Medicine Winders, Tonya A.; Global Patient Platform, Allergy & Asthma Wong, Gary; University of Hong Kong, Paediatrics Xepapadaki, Paraskevi; National and Kapodistrian University of Athens, Allergy Department, 2nd Paediatric Clinic Zar, Heather; University of Cape Town, Department of Paediatrics and Child Health, Red Cross War Memorial Children’s Hospital; Medical Reaserch Council, Unit on Child and Adolescent Health Papadopoulos, Nikolaos; Manchester University NHS Foundation Trust, Division of Infection, Immunity and Respiratory Medicine, ; National and Kapodistrian University of Athens, Allergy Department, 2nd Paediatric Clinic
Keywords:	PAEDIATRICS, Asthma < THORACIC MEDICINE, Paediatric thoracic medicine < PAEDIATRICS, THORACIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.

Authors:

Alexander G. Mathioudakis[1,2,3*], Michael Miligkos[4*], Cristina Boccabella[5], Gioulinta S. Alimani[3,6], Adnan Custovic[7], Antoine Deschildre[8], Francine M. Ducharme[9], Omer Kalayci[10], Clare Murray[1,2], Antonio Nieto Garcia[11], Wanda Phipatanakul[12], David Price[13,14], Aziz Sheikh[15], Ioana Agache[16], Leonard Bacharier[17], Apostolos Beloukas[6,18], Andrew Bentley[1,2], Matteo Bonini[5,19], Jose A. Castro-Rodriguez[20], Giuseppe De Carlo[21], Timothy Craig[22], Zuzana Diamant[23,24,25], Wojciech Feleszko[26], Tim Felton[1,2], James E Gern[27], Jonathan Grigg[28], Gunilla Hedlin[29], Elham M. Hossny[30], Despo Ierodiakonou[31], Tuomas Jartti[32], Alan Kaplan[33], Robert F. Lemanske[27], Peter Le Souef[34], Mika J Makela[35], Georgios A. Mathioudakis[3], Paolo M. Matricardi[36], Marina Mitrogiorgou [37], Mário Morais-Almeida[38], Karthik Nagaraju[39], Effie Papageorgiou[6], Helena Pite[38,40,41], Paulo MC Pitrez[42], Petr Pohunek[43], Graham Roberts[44,45,46], Ioanna Tsiligianni[31], Stephen Turner[47], Susanne, Vijverberg[48], Tonya A. Winders[49,50], Gary Wong[51], Paraskevi Xepapadaki[52], Heather J. Zar[53], Nikolaos G. Papadopoulos[2,52]

* AGM and MM equally contributed to this work.

Affiliations

[1] North West Lung Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK.
[2] Division of Infection, Immunity and Respiratory Medicine, The University of Manchester, Manchester, UK.
[3] Athens Breath Centre, Athens, Greece.
[4] First Department of Pediatrics, University of Athens, "Aghia Sofia" Children's Hospital, Athens, Greece.
[5] Department of Cardiovascular and Thoracic Sciences, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario “A. Gemelli” – IRCCS, Rome, Italy.
[6] Department of Biomedical Sciences, University of West Attica, Athens, Greece.
[7] Department of Paediatrics, Imperial College London, London, UK.
[8] CHU Lille, Université Nord de France, Unité de Pneumologie et Allergologie Pédiatriques, Hôpital Jeanne de Flandre, F-59000 Lille, France.
[9] Departments of Pediatrics and of Social and Preventive Medicine, University of Montreal, Montreal, Canada.
[10] Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, Ankara, Turkey.
[11] Pulmonology and Allergy Unity, University Hospital La Fe, Valencia, Spain.
[12] Children's Hospital Boston, Pediatric Allergy and Immunology, Boston, Massachusetts, USA.
[13] Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK.
[14] Observational and Pragmatic Research Institute, Singapore.
[15] Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK.
[16] Faculty of Medicine, Transylvania University, Brasov, Romania.

[17] Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Washington University, St. Louis, USA.
[18] Institute of Infection and Global Health, University of Liverpool, Liverpool, UK.
[19] National Heart and Lung Institute (NHLI), Imperial College London, UK.
[20] Department of Pediatrics, School of Medicine, Pontifical Universidad Catolica de Chile, Santiago, Chile.
[21] European Federation of Allergy and Airway Diseases Patient's Associations, Brussels, Belgium.
[22] Penn State Allergy, Asthma and Immunology, Hershey, PA, USA.
[23] Department of Respiratory Medicine and Allergology, Institute for Clinical Science, Skane University Hospital, Lund University, Lund, Sweden.
[24] Department of Respiratory Medicine, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic.
[25] Department of Clinical Pharmacy & Pharmacology, University of Groningen, University Medical Center of Groningen and QPS-NL, Groningen, Netherlands.
[26] Department of Pediatric Pulmonology and Allergy, The Medical University Children's Hospital, Warszawa, Poland.
[27] Department of Pediatrics and Medicine, University of Wisconsin School of Medicine and Public Health, Madison, USA.
[28] Centre for Genomics and Child Health, Blizard Institute, Queen Mary University of London, London, UK.
[29] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden.
[30] Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University, Cairo, Egypt.
[31] Health Planning Unit, Department of Social Medicine, Faculty of Medicine, University of Crete, Crete, Greece.
[32] Department of Paediatrics, Turku University Hospital and University of Turku, Turku, Finland.
[33] Family Physician Airways Group of Canada, University of Toronto, Toronto, Ontario, Canada.
[34] School of Paediatrics and Child Health, University of Western Australia, Perth, Australia.
[35] Helsinki University Skin and Allergy Hospital and University of Helsinki, Helsinki, Finland.
[36] Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charité - University Medicine Berlin, Germany.
[37] Third Department of Paediatrics, "ATTIKON" University General Hospital, National and Kapodistrian University of Athens School of Health Sciences, Athens, Greece.
[38] Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal.
[39] VN Allergy & Asthma Research Center, Chennai, Tamilnadu, India
[40] Allergy Center, CUF Infante Santo Hospital, Lisbon, Portugal.
[41] Chronic Diseases Research Center (CEDOC), NOVA Medical School / Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisbon, Portugal.
[42] Laboratory of Respiratory Physiology, Infant Center, School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil.
[43] Paediatric Department, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic.
[44] The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport Isle of Wight, UK.
[45] Faculty of Medicine, Clinical and Experimental Sciences and Human Development in Health Academic Units, University of Southampton, Southampton, UK.
[46] NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK.
[47] Child Health, Royal Aberdeen Children's Hospital and University of Aberdeen, Aberdeen, UK.
[48] Department of Respiratory Medicine and Department of Pediatric Pulmonology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.
[49] Allergy and Asthma Network, Vienna, Virginia, USA.
[50] Global Allergy & Asthma Patient Platform, Vienna, Austria.
[51] Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Sha Tin, Hong Kong.

[52] Allergy Department, 2nd Paediatric Clinic, National and Kapodistrian University of Athens, Athens, Greece.
[53] Department of Paediatrics and Child Health, Red Cross Children's Hospital and SA-Medical Research Council Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa.

Corresponding author:

Professor Nikolaos G. Papadopoulos,

Division of Infection, Immunity & Respiratory Medicine,

The University of Manchester

e-mail: ngpallergy@gmail.com

Phone: +44 161 7016946

Acknowledgement: AGM was supported by the National Institute of Health Research Manchester Biomedical Research Centre (NIHR Manchester BRC). We thank Mrs Maria Kritikou for excellent administrative support of the study.

Abstract

Introduction: Clinical recommendations for childhood asthma are often based on data extrapolated from studies conducted in adults, despite significant differences in mechanisms and response to treatments. The PeARL Think Tank aspires to develop recommendations based on the best available evidence from studies in children. An overview of systematic reviews on pediatric asthma maintenance management and a systematic review of treatments for acute asthma attacks in children, requiring an emergency presentation with/without hospital admission will be conducted.

Methods and analysis: Standard methodology recommended by Cochrane will be followed. Maintenance pharmacotherapy of childhood asthma will be evaluated in an overview of SRs published after 2005 and including clinical trials or real-life studies. For evaluating pharmacotherapy of acute asthma attacks leading to an emergency presentation with/without hospital admission, we opted to conduct de novo synthesis in the absence of adequate up-to-date published SRs. For the SR of acute asthma pharmacotherapy we will consider eligible SRs, clinical trials, or real-life studies without time restrictions. Our evidence updates will be based on broad searches of Pubmed/Medline and the Cochrane Library. We will use AMSTAR-2, Cochrane RoB2 and RELEVANT to evaluate the methodological quality of SRs, controlled clinical trials and real-life studies, respectively.

Next, we will further assess interventions for acute severe asthma attacks with positive clinical results in meta-analyses. We will include both controlled clinical trials and observational studies and will assess their quality using the previously mentioned tools. We will employ random effect models for conducting meta-analyses, and GRADE methodology to assess certainty in the body of evidence.

Ethics and dissemination: Ethics approval is not required for SRs. Our findings will be published in peer reviewed journals and will inform clinical recommendations being developed by the PeARL Think Tank.

Systematic review registration: CRD42020132990, CRD42020171624

Strengths and limitations of this study

- Broad evidence syntheses on the management of childhood asthma, with a focus on the differential treatment response according to age and disease phenotypes could reveal clinically exploitable information, that will be used in the development of clinical and research recommendations by PeARL.
- A rigorous methodology that includes thorough evaluation of the literature, appropriate evaluation of the methodological quality of individual studies and -when appropriate- of the body of evidence, and presentation of overall effect estimates.
- A prospectively published protocol increases the transparency and allowed for peer-review of the methodology utilized.

Keywords: Asthma, Childhood Asthma, Asthma attacks, Asthma attacks in children, Systematic Reviews, Meta-analyses, Overview of Systematic Reviews.

Introduction

Having a global prevalence that is anticipated to exceed 400 million children by the year 2025, childhood asthma represents a huge health and socioeconomic burden to patients, their families and the society[1,2,3]. Despite its diverging mechanisms, triggers, outcomes and response to treatment, childhood asthma is often still approached as an extension of adult asthma[4]. It is under-addressed in clinical guidelines, likely due to unclear diagnosis, limited availability of safety, efficacy and effectiveness data in this population. Clinical recommendations are to a large extent informed by data extrapolated from clinical studies conducted in adults[2,3,4,5].

Numerous challenges complicate conducting interventional research studies in children with asthma. Besides the lack of consensus on its definition and diagnostic criteria, childhood asthma is highly heterogeneous and our understanding of different pediatric asthma phenotypes is still limited or contradictory[6]. This is further emphasized by significant variability in disease progression, outcomes, and treatment response in children with different phenotypes or ages[5,7], potentially complicating interpretation of trials' findings. In addition, there are regulatory and ethical constraints in conducting interventional research in children[8,9]. However, this results in the administration of treatments that have not been adequately evaluated in relevant (pediatric) populations, that is evidently suboptimal.

Pediatric Asthma in Real Life (PeARL), an international Think Tank focusing on Pediatric Asthma, was initiated in the context of the Respiratory Effectiveness Group (REG), to address this evidence deficit. In a recent international, multi-stakeholder survey, we have identified and prioritised unmet needs on pediatric asthma[10]. A need for systematic evidence updates focusing on the management of asthma in different age groups emerged. Herein, we present the protocol for a series of systematic evidence updates aiming to summarise direct evidence from clinical studies in children with asthma, evaluating the safety and clinical effectiveness of pharmacological interventions for maintenance management and for the treatment of acute severe asthma attacks, defined as those leading to an emergency presentation with/without hospital admission, in different age groups. Our work will be used to inform clinical recommendations being developed by the PeARL Think Tank. Therefore, we need solid evidence on the efficacy on safety of various interventions. It is considered crucial to incorporate evidence derived from real-life observational studies, which may carry a lower strength

of evidence than RCTs, but are available in higher abundance and provide a better representation of clinical practice in real life, where for example, treatment compliance or inhaler technique may be problematic.

Methods and analysis

We will conduct two systematic evidence updates, based on protocols prospectively registered in the PROSPERO register (CRD42020132990[11], CRD42020171624[12]). The first will evaluate the safety and clinical effectiveness of pharmacological maintenance treatments for childhood asthma, while the other will focus on the pharmacotherapy of acute severe asthma attacks, defined as those requiring a hospital admission or emergency presentation. We will use standard methodology recommended by the Cochrane Collaboration[13] and will follow the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14].

Preliminary searches revealed several randomized controlled trials evaluating maintenance pharmacotherapy of childhood asthma, which have already been summarised in high-quality systematic reviews (SRs), some conducted by the Cochrane Collaboration. We identified >40 up-to-date SRs evaluating inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA) or biologic therapies, as first line or add-on treatment for asthma in children. As a result, we opted to produce an overview of existing SRs of clinical trials and real-life studies[15].

We found less up-to-date SRs on the management of acute severe asthma attacks in children, mainly focusing on short-acting beta-2 agonists (SABA), short acting muscarinic antagonists (SAMA), oral corticosteroids, aminophylline and magnesium, that were recently summarized in a Cochrane Overview of SRs[16]. However, when evaluating the literature, we identified several other pharmacological interventions that are tested in small trials or real-life studies, often showing promising results, but are not assessed further or introduced in clinical practice guidelines[17,18,19,20,21]. For this reason, we will conduct de novo synthesis of comparative clinical studies of any design aiming to identify any pharmacological intervention that has been tested for acute severe asthma attacks, followed by focused meta-analyses of promising interventions not covered by existing high-quality SRs.

a. **Overview of SRs evaluating maintenance pharmacotherapy for pediatric asthma.**

Eligibility criteria

Eligible studies will comprise SRs and meta-analyses of controlled clinical trials or of real-life studies evaluating maintenance treatments that are broadly used in clinical practice for asthma or recurrent wheeze in children and adolescents, aged up to 18 years. More specifically, we will include SRs comparing any combination of ICS, LABA, LAMA, LTRA, biologic therapies (namely omalizumab, mepolizumab, reslizumab, benralizumab or dupilumab), or placebo as monotherapy or add-on maintenance therapy for pediatric asthma. We will accept SRs and meta-analyses evaluating any molecule of the above-mentioned categories, administered at any dose and for a duration of at least six weeks. SRs comparing asthma maintenance treatment both in children and adults will be included provided that pediatric data are presented separately. We will only include SRs published after 2005 and reported in the English language. Older SRs are probably outdated and will only be considered in the absence of high-quality, newer SRs.

Outcome measures

The primary outcomes of this overview will be the number of acute attacks requiring the administration of oral corticosteroids or an emergency visit, and the number of acute attacks requiring hospitalization. Secondary outcomes will include lung function measures, acute attacks irrespective of the severity, symptom scores (including symptom free and rescue medication free days), asthma control, asthma-specific quality of life scores, use of rescue medications, withdrawal rates (overall, due to lack of efficacy, or adverse events), adverse events and serious adverse events.

Search strategy and study selection

The electronic databases of Medline/PubMed and Cochrane Library will be systematically searched, using appropriate controlled vocabulary and free search terms to identify relevant SRs (terms describing: childhood asthma, LABA, LAMA, LTRA, ICS, biologics, SRs, detailed search strategy is available in the online supplement). Databases will be searched from 2006 onwards. Titles and abstracts of all identified manuscripts, and the full texts of potentially relevant manuscripts, will be screened by two investigators independently. We will report

the reasons of exclusion of studies that will be excluded after full-text review. Disagreement will be resolved through discussion or adjudication by a third investigator, when necessary.

Data abstraction

For each of the included SRs, one investigator will extract the full reference and study identifiers, references of the included trials evaluating pediatric populations, eligibility criteria, predefined outcomes, number and baseline characteristics of the participants and details on the outcomes of interest. A second investigator will cross-check for validity.

Risk of Bias Assessment

AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews, version 2) tool will be used to evaluate the methodological quality of all included SRs[22,23]. The AMSTAR 2 tool evaluates 16 domains, focusing on the methodological design, interpretation and potential risk of bias involved in the conduct of a SR. It is considered by the AMSTAR 2 team that seven domains could critically affect the validity of the review, while the remaining domains describe non-critical weaknesses. Critical flaws for a SR include (i) lack of prospective protocol registration, (ii) inadequate literature searches, (iii) lack of justification of excluding individual studies, (iv) of risk of bias evaluation or (v) of risk of bias consideration in interpreting the results, (vi) of assessment of presence and likely impact of publication bias and (vii) inadequate methodology for conducting meta-analysis. We will consider the results of a SR of high quality, if there is only one or none non-critical weakness, and of moderate quality, if there are more than one non-critical weaknesses. If there are one or more critical weaknesses, then we will consider the confidence low or very low, respectively. Two of the systematic reviewers will evaluate the risk of bias independently and disagreement will be resolved through discussion, or adjudication by a third reviewer.

Qualitative synthesis

We will summarise descriptively or in a tabulated format the characteristics of the included SRs and outcomes of interest. When several SRs evaluate the same intervention, we will compare their eligibility criteria, included studies, and methodological quality as evaluated by the AMSTAR-2 tool, as well as the pertinent subgroup analyses that are presented. We will present in detail the results of the SR that is most recent, more complete

and of high methodological quality. If no single SR fulfil these criteria, we will present in detail more than one SRs. From the remaining SRs, we will present pertinent additional information that may include, such as details about additional outcomes, or additional subgroups.

We will specifically report on the differential effectiveness of the interventions across different maintenance treatment steps (severity), age groups or pediatric asthma phenotypes.

b. **SR of clinical studies evaluating the management of acute severe asthma attacks.**

Over the past decades, several interventions have been tested for the management of acute severe asthma attacks, such as ketamine or macrolide antibiotics[15,16,17,18,19]. Despite promising early findings, some of these interventions were not further tested in robust, prospective controlled clinical trials. This may partially be due to challenges in conducting experimental clinical studies in children, as previously discussed, particularly during acute, life-threatening conditions.

To identify all evaluated treatments, a two-stage approach will be followed. Firstly, a broad search strategy will be used to identify all pharmacological interventions that have been tested as potential treatments for acute severe asthma attacks. Next, medications that showed positive clinical results, but are not yet recommended by clinical practice guidelines, will be selected and further evaluated in individual meta-analyses.

Broad SR

Medline/PubMed and the Cochrane Library will be searched, using a broad search strategy, aimed to identify any clinical research studies evaluating the management of acute severe asthma attacks (detailed search strategy is available in the online supplement).

Any study evaluating pharmacological treatments for acute severe asthma attacks in children and adolescents (< 18 years of age) will be included. Any comparative clinical research study, including experimental and

observational studies, as well as SRs of such studies will be considered eligible for inclusion. We will only include studies reported in the English language, without time restrictions.

Eligible studies will be grouped according to the drug category they evaluate and will be presented narratively. Study design, characteristics and outcomes of interest will be reported descriptively or in a tabulated format. Outcomes of interest are the same for this broad SR and individual medication meta-analyses and are detailed in the next section.

Individual medication meta-analyses

These meta-analyses will further evaluate the safety and clinical effectiveness of individual medications that were assessed by the initial broad SR and were found to be of potential clinical value for the treatment of acute severe asthma attacks. In contrast to most preceding SRs and meta-analyses, we will include data from observational comparative effectiveness (real-life) studies, as well as controlled clinical trials.

Eligibility criteria

For each meta-analysis, eligible studies will comprise controlled clinical trials and observational comparative effectiveness studies comparing the index medication with placebo, no treatment or any active control, as an add-on treatment for acute severe asthma attacks. Index medication will be defined based on the pharmacological action, meaning that molecules targeting the same pharmacological target (e.g. salbutamol and terbutaline, both being short-acting beta-2 agonists) will be grouped. Only studies evaluating the management of acute severe asthma attacks, defined as those requiring a hospital admission or emergency presentation, in children and adolescents, aged between 1 and 18 years of age will be included. Studies evaluating both children and adults will be included, provided that pediatric data are reported separately or that we will be able to access these data after requesting them from the investigators. We will only include observational studies that meet the primary criteria of the RELEVANT tool (see risk of bias). There will be no time or language restrictions.

Outcome measures

The primary outcome measures will be (i) treatment success or treatment failure rate within 2 weeks from presentation, (ii) serious adverse events and, (iii) need for asthma related hospitalization within 2 weeks from presentation. Treatment success will be defined as a complete resolution of the symptoms, or an improvement in the clinical signs, symptoms and/or laboratory findings that fulfils specific criteria or thresholds prespecified by the study team. Treatment failure will be defined as a significant deterioration of the patients' clinical conditions that fulfils specific criteria prespecified by the study team. For example, treatment failure may be defined as the need for paediatric intensive care unit admission, ventilation, or death. Need for asthma related hospitalization will not be relevant for studies only evaluating hospitalized participants. Secondary outcomes will include (i) mortality, (ii) duration of asthma-related hospitalization, (iii) need for intensive care unit admission, (iv) duration of intensive care unit stay, (v) re-exacerbation rate, (vi) re-hospitalization rate, (vii) adverse events. All outcomes will be evaluated at a maximum follow-up of 6 months, as longer-term outcomes are less likely to be directly linked with the index acute event.

Search strategy and study selection

Using appropriate controlled vocabulary and free search terms, we will systematically search Medline/ Pubmed, EMBASE and the Cochrane Library to identify controlled clinical trials and observational comparative effectiveness studies evaluating the safety, efficacy and/or clinical effectiveness of the selected medication (sample search strategies are available in the online appendix). We will also search the World Health Organization International Clinical Trials Registry Platform (ICTRP) search portal, the abstract proceedings of the European Respiratory Society, the American Thoracic Society, the Asian Pacific Society of Respirology, the European Academy of Allergy and Clinical Immunology, the American Academy of Allergy, Asthma and Immunology, and the World Allergy Organization, as well as the reference lists of all included studies. All sources will be searched from inception, without language limitations. We will follow standard methodology for screening titles, abstracts and the full text of all identified studies, as described previously.

Data abstraction

The full study reference, study identifiers, details on the study design, eligibility criteria, predefined outcomes and potential confounding factors that were considered by the investigators, number and baseline characteristics of participants will be extracted by one investigator and will be cross-checked for validity by a

second extractor. Details on the outcomes of interest from all included studies will be extracted by two investigators independently. Conflicts will be resolved through discussion and when needed adjudication by a third investigator.

Risk of bias of individual studies

We will use the second version of the Cochrane risk of bias (RoB2) tool for assessing risk of bias in the included RCTs[24] and the REal Life EVidence AssessmeNt Tool (RELEVANT) for assessing the risk of bias of observational studies[25]. Risk of bias of each included study will be evaluated by two investigators independently.

The RoB2 tool evaluates the following domains for potential risk of bias: (i) bias arising from the randomization process, (ii) bias due to deviations from intended interventions, (iii) bias due to missing outcome data, (iv) bias in measurement of the outcome, (v) bias in selection of reported results and (vi) any other potential source of bias. High risk of bias in any of these domains will result in an overall judgement of high risk of bias. In the absence of high-risk domains, unclear risk in any domain will lead to an overall judgement of unclear risk. All remaining trials will be considered to be of low risk of bias.

RELEVANT evaluates the quality of observational comparative effectiveness research studies across seven domains, which include background, design, measures, analysis, results, discussion/interpretation and conflicts of interest. Each domain includes primary and secondary items. It is suggested that studies not meeting the primary items of RELEVANT are of very low methodological quality (have “fatal flaws”) and should not be used to inform clinical recommendations. Therefore, we will exclude studies not meeting these criteria. We will consider of low risk of bias all studies meeting the secondary criteria of RELEVANT as well, and of high risk of bias studies that do not meet any of the secondary criteria.

For every comparison, we will use funnel plots, Egger’s regression and Begg’s rank tests to evaluate publication bias, if we are able to pool more than 10 studies.

Data synthesis

Data from controlled clinical trials or observational studies will be analysed separately. In addition, studies evaluating different comparators, will be analysed separately. If different doses of the index medication or

comparator are evaluated across the included studies, we will consider grouping studies using similar doses, providing that their results are not significantly dissimilar.

For every analysis, I^2 statistic will be used to assess statistical heterogeneity. Substantial heterogeneity (I^2> 50%) will be explored using prespecified subgroup analyses (details in the next section). We will not perform meta-analyses in cases of considerable unresolved heterogeneity (I^2 >75%).

Meta-analyses will be performed using the random-effects model, because we anticipate significant heterogeneity in our data. Results will be presented in the form of relative risk (RR, 95% confidence intervals – CI) for dichotomous data, mean difference (MD, 95% CI) for continuous data and hazard ratios (HR, 95% CI) for time to event data. Meta-analyses will be performed using Review Manager version 5 (RevMan, http://community.cochrane.org/tools/review-production-tools/revman-5) and R statistics version 3.4.3 or newer (R Foundation for Statistical Computing, Vienna, Austria).

For dichotomous outcomes, the unit of analysis will preferably be participants, rather than events (i.e. number of participants admitted to the intensive care unit, rather than number of admissions per participants).

Sensitivity and subgroup analyses

In sensitivity analyses for all comparisons, we will (i) use fixed effects models, (ii) only include studies with low risk of bias, (iii) exclude studies reporting limited adherence to the study drugs (<80%), and (iv) evaluate separately studies assessing different doses of the index medication, which we may pool in the main analysis.

Subgroup analyses according to participants' age, asthma phenotypes or, possibly, acute attack phenotypes will also by conducted, depending on data availability. In an additional subgroup analysis, we will evaluate separately trials utilising exploratory versus pragmatic study designs.

Certainty of the body of evidence

Certainty of the body of evidence, for every comparison will be evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology[26]. GRADE assesses the certainty in a body of evidence as high, moderate, low, or very low after considering the methodological quality of the included studies, imprecision, inconsistency, indirectness, publication bias, the magnitude of effect, dose response, and confounders likely to minimize the effect. All decisions to upgrade or downgrade the quality of

evidence will be transparent and justified in evidence profile and summary of evidence tables, in accordance with GRADE guidance. GRADEPro Software (2014; www.gradepro.org) will be used for the development of these tables.

We will use GRADE methodology to assess the risk of bias associated with missing participant outcome data across the body of the available evidence[27]. GRADE suggests repeating the primary meta-analysis, imputing the most extreme assumptions about the values of the missing data, that the investigators consider plausible. Only if the analyses prove robust to this imputation, the risk of bias due to missing participant outcome data should be deemed low.

The impact that the risk of bias of individual studies and the confidence in the body of the evidence has on the results will be presented.

Ethics and dissemination

Ethical approval is not required for these SRs, since no primary data will be collected.

The findings of these evidence updates will be presented in national and international scientific conferences. They will also be submitted for publication in high-impact peer review journals. Moreover, our results will be used to inform clinical recommendations that will be developed by the PeARL Think Tank.

Patient and public involvement

The planned systematic reviews were prioritized through a global, multi-stakeholder survey evaluating research priorities in childhood asthma, conducted by the PeARL think tank[10]. Among other stakeholders, this survey included responses from patients, patient caregivers and patient organizations.

Discussion

We report on the methodology of a series of planned systematic evidence updates, aiming to evaluate maintenance management of childhood asthma, and the treatment of acute severe asthma attacks. Their

design is informed by preliminary searches and the anticipated data availability. These SRs will be conducted by the PeARL group and will be used to inform clinical recommendations and future research needs. The need for high-quality evidence updates and clinical practice guidelines to improve the management of asthma in children is more urgent now, given the pressure that the unfolding coronavirus disease 19 (COVID-19) pandemic pose on the health care systems, forcing us to reconsider our daily clinical practice[28,29].

Major strengths of our evidence update series are the inclusion of a wide evidence base, including data from RCTs and real-life comparative studies, the prospective design and strong methodology. The methodological quality of all available studies will be scrutinized and will aid the interpretation of our findings. Moreover, we will attempt to evaluate differential therapeutic response of different asthma phenotypes and age groups. We believe this analysis will be revealing, if adequate data is available, but may nevertheless reveal important gaps.

Guided by the available evidence, we will follow different strategies for the evidence updates on maintenance treatment of pediatric asthma and on management of acute severe asthma attacks. In view of the availability of ample published, up-to-date SRs on maintenance pharmacotherapy of childhood asthma, we chose to conduct an overview of SRs. We decided to focus on the most frequently used and thoroughly evaluated drug classes (ICS, LABA, LAMA, LTRA, and biologic therapies) and we expect to identify good quality data, which would inform clinical practice and research needs. Other, less frequently or experimentally used treatments will need to be evaluated in future studies.

The second SR, focusing on the management of acute attacks, will first evaluate a multitude of established and experimental treatments. With regards to the later, this SR will reveal treatments that have been tested, appeared safe and efficacious and it may be worth to be further evaluated, but will also report on interventions that were tested, but did not appear efficacious, and therefore, further evaluation may not be beneficial. This wide approach would aid the prioritisation of interventions to be further validated in future clinical research studies.

Next, meta-analyses of individual pharmacological interventions will be conducted to further assess the safety and clinical effectiveness of treatments for acute severe asthma attacks that will appear efficacious in our broad SR. In contrast to most previous meta-analyses, that may have been conducted, we will include both

controlled clinical trials and observational comparative effectiveness studies. Due to limitations that have already been discussed, few controlled clinical trials are conducted in children. This leads several Cochrane SRs to report low or very low confidence in the body of evidence, due to the lack of data[30,31,32,33]. We believe that by incorporating data from observational studies we may be able to conclude more robust results. While observational studies are at a higher risk of bias, we will carefully evaluate this risk using the newly developed, thorough RELEVANT tool and we will discuss potential implications on our findings. The GRADE working groups provides transparent guidance for assessing the certainty in a body of evidence including data from different study designs (controlled clinical trials or observational studies); this guidance will be used for interpreting the findings of our meta-analyes.

Overall, we aim to develop evidence updates on the maintenance treatment of asthma and management of acute severe asthma attacks, that will cover all available evidence, carefully considering methodological limitations. These will be used by the PeARL Think Tank for the development of clinical recommendations and to guide future clinical research.

Author contribution: Study conception: AGM, NGP. Study design: AGM, MM, NGP. Preparation of the manuscript: AGM. Critical revision of the manuscript: All authors. Final approval of the manuscript: All authors.

Declaration of Interests: *This study was supported by the Respiratory Effectiveness Group (REG). None of the authors had any conflicts of interest directly related to this work. MM, GSA, IA, AB, AB, AB, MB, GDC JACR, WF, GC, GH, EMH, DI, TJ, OK, MJM, GAM, PMM, MM, MM-A, KN, EP, ANG, HP, PMCP, SS-G PLS, AS, ST, SV, TW, GW, HZ do not declare any conflicts of interest outside the submitted work either. AGM reports grants from Boehringer Ingelheim outside the submitted work. AC reports personal fees from Novartis, Regeneron / Sanofi, Thermo Fisher Scientific, Boehringer Ingelheim and Philips, outside the submitted work. LB reports personal fees from Aerocrine, GlaxoSmithKline, Genentech/Novartis, Merck, DBV Technologies, Teva, Boehringer Ingelheim, AstraZeneca, WebMD/Medscape, Sanofi/Regeneron, Vectura and Circassia outside the submitted work. TC reports grants and personal fees CSL Behring, Dyax, Takeda, BioCryst, Pharming, personal fees from Grifols, grants and non-financial support from GSK, Regeneron, Novartis/Genetech outside the submitted work. AD reports grants and personal fees from Stallergenes Greer, personal fees from Novartis, ALK, TEVA, GSK, MEDA-MYLAN, CHIESI, AImmune, DBV technologies and Astra Zeneca, outside the submitted work. ZD reports personal fees from academic affiliations, ZD acts as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies. ZD reports personal fees from Astrazeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD, and Sanofi-Genzyme outside the submitted work. FMD reports grants from Thorasys Inc; personal fees from Jean-Coutu Pharmaceuticals, unrestricted research funds from Novartis Canada, Teva and Trudell Medical, research grants* from GlaxoSmithKline and MEDteq in partnership with Thorasys Inc.; honorarium for consultancy work from Covis Pharma and Teva; and honorarium as invited speaker from Covis Pharma, Pharmacy Brunet, *outside the submitted work. JEG reports grants from NIH/NIAID, personal fees from Regeneron, Ena Theraputics and MedImmune outside the submitted work; personal fees and stock options from Meissa Vaccines Inc outside the*

submitted work. JG reports personal fees from GSK, Vifor Pharmaceuticals, Novartis, BV Pharma and AstraZeneca outside the submitted work. AK reports personal fees Astra Zeneca, Behring, Boehringer Ingelheim, Covis, GSK, NovoNordisk, Novartis, Griffols, Pfizer, Sanofi, Teva and Trudel, outside the submitted work. RFL reports grants from NIH, non-financial support from GlaxoSmithKline, Boehringer-Ingelheim, Merck, TEVA, American Academy of Allergy, Asthma and Immunology, grants from Clinical and Translational Science Award (NIH), Childhood Origins of ASThma (COAST) grant , AsthmaNet, personal fees from LSU, Elsevier, UpToDate, the University of Kentucky, ThermoFischer, and Food Allergy Research and Education (FARE) Network, outside the submitted work. CM reports personal fees from Novartis, GSK, Astra Zeneca, Thermo Fisher and Boehringer Ingelheim outside the submitted work. NGP reports personal fees from ALK, Novartis, Nutricia, HAL, Menarini/FAES Farma, Sanofi, Mylan/MEDA, Biomay, AstraZeneca, GSK, MSD, ASIT BIOTECH and Boehringer Ingelheim; grants from Gerolymatos International SA and Capricare outside the submitted work. WP reports grants from NIH; grants and personal fees from Genentech/Novartis, Sanofi/Rgeneron; personal fees GSK; non-financial support from Thermo Fisher, Lincoln Diagnostics, Alk Abello, and Monaghen, outside the submitted work. PP reports grants from Astra Zeneca, Chiesi and TEVA; personal fees from Astra Zeneca, TEVA, Novartis, Mundipharma, S&D Pharma, and GlaxoSmithKline outside the submitted work. DP reports grants from AKL Research and Development Ltd, British Lung Foundation, Respiratory Effectiveness Group and the UK National Health Service; grants and personal fees from Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, TEVA, Theravance, and Zentiva (Sanofi Generics); personal fees from Cipla, GlaxoSmithKline, Kyorin, and Merck; non-financial support from Efficacy and Mechanism Evaluation programme, Health Technology Assessment, outside the submitted work; DP also reports stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; and owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore), outside the submitted work. GCR reports personal fees from ALK, Allergen Therapeutics, Meda Plus, Merck; and a patent for the use of sublingual immunotherapy to prevent the development of allergy in at-risk infants, outside the submitted work. IT reports personal fees from Novartis, GSK, Boehringer Ingelheim, and Astra Zeneca; grants from GSK Hellas, outside the submitted work. PX reports personal fees from Nutricia, Nestle, Friesland, Uriach, Novartis Pharma AG, and GlaxoSmithkline outside the submitted work.

Funding: This work was supported by the Respiratory Effectiveness Group (REG). REG has received support from AstraZeneca, Novartis and Sanofi for continued work on PeARL. (Award/Grant name: PeARL, Award/Grant Number: N/A). This is an investigator initiated study and the funders were not involved in the selection of the topic, or design of these systematic reviews.

References:

[1] To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12: 204. https://doi.org/10.1186/1471-2458-12-204.

[2] Global Initiative for Asthma. GINA guidelines. Global strategy for Asthma Management and Prevention. Available at: www.ginasthma.org (accessed March 1, 2018).

[3] British Thoracic Society, Scottish Intercollegiate Guidelines Network. SIGN 158: British guideline on the management of asthma. BTS/SIGN, Edinburgh, 2019.

[4] Papadopoulos NG, Čustović A, Cabana MD, Dell SD, Deschildre A, Hedlin G, et al. Pediatric asthma: An unmet need for more effective, focused treatments. Pediatr Allergy Immunol. 2019 Feb;30(1):7-16. doi: 10.1111/pai.12990.

[5] Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R, et al. International consensus on (ICON) pediatric asthma. Allergy. 2012 Aug;67(8):976-97.

[6] Kwong CG, Bacharier LB. Phenotypes of wheezing and asthma in preschool children. Curr Opin Allergy Clin Immunol. 2019 Apr;19(2):148-153.

[7] Tse SM, Krajinovic M, Chauhan BF, Zemek R, Gravel J, Chalut D, et al. Genetic determinants of acute asthma therapy response in children with moderate-to-severe asthma exacerbations. Pediatr Pulmonol. 2019;54(4):378-385.
[8] Multidisciplinary scientific guidelines: paediatrics http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000404.jsp&mid=WC0b01ac0580029572 (2013).
[9] Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Global Research in Paediatrics. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014 Jun;73:2-13.
[10] Mathioudakis AG, Custovic A, Deschildre A, Ducharme FM, Kalayci O, Murray C, et al. Research priorities in pediatric asthma: Results of a global survey of multiple stakeholder groups by the Pediatric Asthma in Real Life (PeARL) Think Tank. *J Allergy Clin Immunol Pract 2020. In Press.*
[11] Mathioudakis AG, Miligkos M, Papadopoulos NG. Maintenance treatment for childhood asthma: A protocol for an overview of systematic reviews by the PeARL think-tank. International prospective register of systematic reviews (PROSPERO). 2020. CRD42020132990
[12] Mathioudakis AG, Alimani GS, Papadopoulos NG. Pharmacological management of acute severe asthma attacks in children. Protocol for a systematic review by the PeARL think tank. International prospective register of systematic reviews (PROSPERO). 2020. CRD42020171624.
[13] Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. 2011.
[14] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-12.
[15] Thomson D, Russell K, Becker L, Klassen T, Hartling L. The evolution of a new publication type: steps and challenges of producing overviews of reviews. Research Synthesis Methods 2010; 1: 13.
[16] Craig SS, Dalziel SR, Powell CV, Graudins A, Babl FE, Lunny C. Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2020 Aug 5;8:CD012977. doi: 10.1002/14651858.CD012977.pub2.
[17] Katsunuma T, Fujisawa T, Maekawa T, Akashi K, Ohya Y, Adachi Y, et al. Low-dose L-Isoproterenol Versus Salbutamol in Hospitalized Pediatric Patients With Severe Acute Exacerbation of Asthma: A Double-Blind, Randomized Controlled Trial. Allergol Int. 2019; 68(3), 335-341.
[18] Elkoundi A, Bentalha A, El Koraichi A, El Kettani SE. Nebulized ketamine to avoid mechanical ventilation in a pediatric patient with severe asthma exacerbation. Am J Emerg Med. 2018 Apr;36(4):734.e3-734.e4. doi: 10.1016/j.ajem.2018.01.027.
[19] Douglas LC, Choi J, Esteban-Cruciani N. Azithromycin treatment in children hospitalized with asthma: a retrospective cohort study. J Asthma. 2020 May;57(5):525-531. doi: 10.1080/02770903.2019.1590590. Epub 2019 Apr 1. PMID: 30929521.
[20] Wong JJ, Lee JH, Turner DA, Rehder KJ. A review of the use of adjunctive therapies in severe acute asthma exacerbation in critically ill children. Expert Rev Respir Med. 2014 Aug;8(4):423-41.
[21] Mathioudakis A, Chatzimavridou-Grigoriadou V, Evangelopoulou E, Mathioudakis G. Vasoactive intestinal Peptide inhaled agonists: potential role in respiratory therapeutics. Hippokratia. 2013 Jan;17(1):12-6.
[22] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008.
[23] Pollock M, Fernandes R, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions. BMC Medical Research Methodology 2017b; 17: 13.
[24] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.
[25] Campbell JD, Perry R, Papadopoulos NG, Krishnan J, Brusselle G, Chisholm A, et al. The REal Life EVidence AssessmeNt Tool (RELEVANT): development of a novel quality assurance asset to rate observational comparative effectiveness research studies. Clin Transl Allergy. 2019 Mar 27;9:21.
[26] Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6.
[27] Guyatt GH, Ebrahim S, Alonso-Coello P, Johnston BC, Mathioudakis AG, Briel M, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. J Clin Epidemiol. 2017 Jul;87:14-22.
[28] Papadopoulos NG, Custovic A, Deschildre A, Mathioudakis AG, Phipatanakul W, Wong G, et al. Impact of COVID-19 on Pediatric Asthma: Practice Adjustments and Disease Burden. J Allergy Clin Immunol Pract. 2020 Sep;8(8):2592-2599.e3. doi: 10.1016/j.jaip.2020.06.001.
[29] Papadopoulos NG, Mathioudakis AG, Custovic A, Deschildre A, Phipatanakul W, Wong G, et al. Childhood asthma during the COVID-19 pandemic: Findings from the PeARL multi-national cohort. Allergy. In peer review.
[30] Vézina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. Cochrane Database Syst Rev. 2014 Jul 31;(7):CD010283.

[31] Normansell R, Kew KM, Mathioudakis AG. Interventions to improve inhaler technique for people with asthma. Cochrane Database Syst Rev. 2017 Mar 13;3:CD012286.
[32] Normansell R, Kew K, Stovold E, Mathioudakis AG, Dennett E. Interventions to improve inhaler technique and adherence to inhaled corticosteroids in children with asthma. Paediatr Respir Rev. 2017 Jun;23:53-55.
[33] Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2017 Nov 28;11:CD003898.

Online Appendix

Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.

Search Strategies

1. Overview of SRs evaluating stable asthma treatment

#1 Asthma [MH]

#2 Respiratory Sounds[MH]

#3 Bronchial spasm [MH]

#4 Bronchial Hyperreactivity [MH]

#5 Respiratory Hypersensitivity [MH]

#6 Anti-asthmatic agents[MH]

#7 Asthma [tiab]

#8 Wheez* [tiab]

#9 Bronchospas* [tiab]

#10 Bronchoconstrict* [tiab]

#11 Bronch* [tiab] and (constrict* [tiab])

#12 (bronchial* [tiab] or (respiratory[tiab]) or (airway* [tiab]) or (lung* [tiab])) and (hypersensitiv* [tiab] or (hyperreactiv* [tiab]) or (allerg* [tiab]))

#13 OR / 1-12

#14 (Steroid* [tiab] or (corticosteroid* [tiab]) or (glucocorticoid* [tiab])) and (inhal* [tiab])

#15 Beclomethasone [MH]

#16 Budesonide [MH]

#17 Fluticasone [MH]

#18 Mometasone Furoate [MH]

#19 Triamcinolone [MH]

#20 Beclomethasone [tiab]

#21 Beclometasone [tiab]

#22 Budesonide [tiab]

#23 Fluticasone [tiab]

#24 Ciclesonide [tiab]

#25 Mometasone [tiab]

#26 Flunisolide [tiab]

#27 Triamcinolone [tiab]

#28 ICS [tiab]

#29 OR/ 14-28

#30 Adrenergic beta-2 receptor Agonists [MH] and (inhal* [tiab])

#31 Beta-agonist* [tiab] and (inhal* [tiab])

#32 Salmeterol Xinafoate [MH]

#33 Formoterol Fumarate [MH]

#34 Clenbuterol [MH]

#35 Salmeterol [tiab]

#36 Formoterol [tiab]

#37 Vilanterol [tiab]

#38 Indacaterol [tiab]

#39 Clenbuterol [tiab]

#40 Olodaterol [tiab]

#41 Bambuterol [tiab]

#42 *formoterol [tiab]

#43 LABA [tiab]

#44 OR/ 30-43

#45 Muscarinic antagonists [MH] and (inhal* [tiab])

#46 Tiotropium Bromide [MH]

#47 Tiotropium [tiab]

#48 Umeclidinium [tiab]

#49 GSK573719 [tiab]

#50 Aclidinium [tiab]

#51 LAS34273 [tiab]

#52 Glycopyrronium [tiab]

#53 NVA237 [tiab]

#54 LAMA [tiab]

#55 Muscarinic* [tiab] and (Antagonist* [tiab]) and (inhal* [tiab])

#56 Antimuscarinic* [tiab]

#57 OR/ 45-56

#58 Leukotriene Antagonists[MH]

#59 Leukotriene* [tiab] AND (Antagonist* [tiab])

#60 Anti-leukotriene* [tiab]

#61 Anti-leucotriene [tiab]

#62 Montelukast [tiab]

#63 Zafirlukast [tiab]

#64 Pranlukast [tiab]

#65 LTRA [tiab]

#66 OR/ 58-65

#67 Biological Factors [MH]

#68 Omalizumab [MH]

#69 Omalizumab [tiab]

#70 Mepolizumab [tiab]

#71 Benralizumab [tiab]

#72 Reslizumab [tiab]

#73 Dupilumab [tiab]

#74 OR/ 67-73

#75 meta-analysis [Publication type] *HIRU Filter for Systematic Reviews*

#76 meta-analysis [MH]

#77 meta-analysis [tiab]

#78 review [Publication type]

#79 search*[tiab]

#80 OR/ 75-79

#81 #28 OR #44 OR #57 OR #66 OR #74

#82 #13 AND #80 AND #81

#83 children [MH] or (adolescents [MH])

#84 adults [MH] NOT #75

#85 Editorial [publication type]

#86 Letter [publication type]

#87 #82 NOT (#84 OR #85 OR #86)

2. Severe asthma exacerbations treatment: Broad systematic review

#1 Asthma [MH]

#2 Severe asthma [MH]

#3 Brittle asthma [MH]

#4 Asthma [tiab]

#5 OR/ 1-4

#6 Disease Exacerbation [MH]

#7 Exacerbation [tiab]

#8 Exacerbation* [tiab]

#9 Attack [tiab]

#10 Acute [tiab]

#11 OR/ 6-10

#12 Intensive care [MH]

#13 Severe [tiab]

#14 Refractory [tiab]

#15 Near fatal [tiab]

#16 Life-threatening [tiab]

#17 Difficult-to-treat [tiab]

#18 Therapy resistant [tiab]

#19 Intensive care[tiab]

#20 Critically ill [tiab]

#21 ICU [tiab]

#22 OR/ 12-21

#23 (#5 AND #11 AND #22)

#24 Status asthmaticus[MH]

#25 Status asthmaticus[tiab]

#26 (#23 OR #24 OR #25)

#27 (animals [mh] NOT humans [mh])

#28 children [MH] or (adolescents [MH])

#29 adults [MH] NOT #28

#30 Review [publication type]

#31 Systematic review [publication type]

#32 Meta-analysis[publication type]

#33 (#30 NOT (#31 or #32))

#34 Letter [publication type]

#35 Editorial [publication type]

#36 (#26 NOT (#27 OR #29 OR #33 OR #34 OR #35))

3. Severe asthma exacerbations treatment: Individual medication meta-analyses

#1 Asthma [MH]

#2 Respiratory Sounds[MH]

#3 Bronchial spasm [MH]

#4 Bronchial Hyperreactivity [MH]

#5 Respiratory Hypersensitivity [MH]

#6 Anti-asthmatic agents[MH]

#7 Asthma [tiab]

#8 Wheez* [tiab]

#9 Bronchospas* [tiab]

#10 Bronchoconstrict* [tiab]

#11 Bronch* [tiab] and (constrict* [tiab])

#12 (bronchial* [tiab] or (respiratory[tiab]) or (airway* [tiab]) or (lung* [tiab])) and (hypersensitiv* [tiab] or (hyperreactiv* [tiab]) or (allerg* [tiab]))

#13 OR / 1-12

#14 Search terms related to the medication under investigation, including MeSH terms and free search terms.

#15 children [MH]

#16 paediatric*[tiab]

#17 pediatric* [tiab]

#18 child* [tiab]

#19 adolescen* [tiab]

#20 infant* [tiab]

#21 toddler* [tiab]

#22 preschool* [tiab]

#23 OR/ 16-22

#24 #13 AND #14 AND #23

#25 (animals [mh] NOT humans [mh])

#26 children [MH] or (adolescents [MH])

#27 adults [MH] NOT #26

#28 Review [publication type]

#29 Systematic review [publication type]

#30 Meta-analysis[publication type]

#31 (#28 NOT (#29 OR #30))

#32 Letter [publication type]

#33 Editorial [publication type]

#34 (#24 NOT (#25 OR #27 OR #31 OR #32 OR #33))

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	124
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-95
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	439-440
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	487-490
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	487-490
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	487-490
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	143-170
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	158-170

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	196-213, 282-306
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	214-221, 265-267, 308-317
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	215-218, 308-311, Online appendix
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	218-221, 316-317
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	218-221, 316-317
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	222-226, 318-324
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	269-273, 365-371
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	269-273, 365-371
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	227-240, 325-343.
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	272-275, 344-359
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	349-351
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	249-250, 360-366

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	241-250
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	342-343, 367-382
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	367-382

BMJ Open

Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048338.R1
Article Type:	Protocol
Date Submitted by the Author:	13-May-2021
Complete List of Authors:	Mathioudakis, Alexander; The University of Manchester, Division of Infection, Immunity and Respiratory Medicine; Manchester University NHS Foundation Trust, North West Lung Centre Miligkos, Michael ; University of Athens, First Department of Pediatrics, "Aghia Sofia" Children's Hospital, Boccabella, Cristina; Catholic University of the Sacred Heart, Department of Cardiovascular and Thoracic Sciences Alimani, Gioulinta; University of West Attica, Department of Biomedical Sciences; Athens Breath Centre, Pulmonology Custovic, Adnan; Imperial College London, Department of Paediatrics Deschildre, A.; CHU Lille, Unité de Pneumologie et Allergologie Pédiatriques, Hôpital Jeanne de Flandre, F-59000 Lille, France. Ducharme, Francine; University of Montreal, Pediatrics Kalayci, Omer; Hacettepe Universitesi, Pediatric Allergy and Asthma Unit Murray, Clare ; The University of Manchester, Division of Infection, Immunity and Respiratory Medicine, ; North West Lung Centre, Wythenshawe Hospital Garcia, Antonio; La Fe University and Polytechnic Hospital, Pulmonology and Allergy Unity Phipatanakul, Wanda; Children's Hospital Boston, Pediatric Allergy and Immunology Price, David; University of Aberdeen, Centre of Academic Primary Care Sheikh, Aziz; The University of Edinburgh, Division of Community Health Sciences Agache, Ioana; Transylvania University, Allergy and Clinical Immunology Bacharier, Leonard; University of Washington, Department of Immunology, and Pulmonary Medicine Beloukas, Apostolos; University of West Attica, Department of Biomedical Sciences; University of Liverpool Institute of Infection and Global Health, University of Liverpool Bentley, Andrew; University Hospital of South Manchester NHS Foundation Trust, Acute Intensive Care Unit; University Hospital of South Manchester NHS Foundation Trust, North West Lung Centre Bonini, Matteo; Catholic University of the Sacred Heart, Department of Cardiovascular and Thoracic Sciences; Imperial College London, Department of Cardiovascular and Thoracic Sciences Castro-Rodriguez, Jose A.; University of Chile, Department of Pediatrics De Carlo, Giuseppe; European Federation of Pharmaceutical Industries and Associations, Allergy and Airway Diseases Patient's Associations

	Craig, Timothy; Penn State, Asthma and Immunology Diamant, Z.; Skane University Hospital Lund Hematological Clinic, Department of Respiratory Medicine and Allergology, Institute for Clinical Science; Charles University, Department of Respiratory Medicine Prague Feleszko, Wojciech ; Medical University of Warsaw, Department of Pediatric Pulmonology and Allergy Felton, Tim; University of Manchester, Division of Infection, Immunity and Respiratory Medicine Gern, James; University of Wisconsin Colleges, Department of Pediatrics and Medicine Grigg, Jonathan; Queen Mary University of London, Paediatric Respiratory Hedlin, Gunilla; Karolinska Institute, Department of Women's and Childnren's Health Hossny, Elham M.; Ain Shams University, Pediatric Allergy and Immunology Unit Ierodiakonou, Despo; University of Crete, Department of Social Medicine Jartti, Tuomas; University of Turku, Department of Paediatrics Kaplan, Alan; Canada, Family Physician Lemanske, Robert F.; University of Wisconsin System, Department of Pediatrics and Medicine Le Souëf, Peter; University of Western Australia, Discipline of Paediatrics Mäkelä, Mika; University of Helsinki, Department of Allergy Mathioudakis, Georgios; Athens Breath Centre, Pulmonology Matricardi, Paolo; Charite Universitatsmedizin Berlin Mitrogiorgou, Marina; National and Kapodistrian University of Athens School of Health Sciences, Third Department of Paediatrics Morais-Almeida, Mario; Hospital CUF Descobertas, Allergy Center Nagaraju, Karthik; VN, Allergy & Asthma Papageorgiou, Effie; University of West Attica, Department of Biomedical Sciences Pité, H; Hospital CUF Descobertas, Allergy Center Pitrez, Paulo MC; Charite University Hospital Berlin, Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Pohunek, Petr; Motol University Hospital, Paediatric Department Roberts , Graham ; University of Southampton, Faculty of Medicine Tsiligianni, Ioanna; University of Crete Faculty of Medicine, Clinic of Social and Family Medicine Turner, Stephen; University of Aberdeen, Department of Child Health Susanne, Vijverberg; University of Amsterdam, Department of Respiratory Medicine Winders, Tonya A.; Global Patient Platform, Allergy & Asthma Wong, Gary; University of Hong Kong, Paediatrics Xepapadaki, Paraskevi; National and Kapodistrian University of Athens, Allergy Department, 2nd Paediatric Clinic Zar, Heather; University of Cape Town, Department of Paediatrics and Child Health, Red Cross War Memorial Children’s Hospital; Medical Reaserch Council, Unit on Child and Adolescent Health Papadopoulos, Nikolaos; Manchester University NHS Foundation Trust, Division of Infection, Immunity and Respiratory Medicine, ; National and Kapodistrian University of Athens, Allergy Department, 2nd Paediatric Clinic
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Respiratory medicine
Keywords:	PAEDIATRICS, Asthma < THORACIC MEDICINE, Paediatric thoracic medicine < PAEDIATRICS, THORACIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.

Authors:

Alexander G. Mathioudakis[1,2,3*], Michael Miligkos[4*], Cristina Boccabella[5], Gioulinta S. Alimani[3,6], Adnan Custovic[7], Antoine Deschildre[8], Francine M. Ducharme[9], Omer Kalayci[10], Clare Murray[1,2], Antonio Nieto Garcia[11], Wanda Phipatanakul[12], David Price[13,14], Aziz Sheikh[15], Ioana Agache[16], Leonard Bacharier[17], Apostolos Beloukas[6,18], Andrew Bentley[1,2], Matteo Bonini[5,19], Jose A. Castro-Rodriguez[20], Giuseppe De Carlo[21], Timothy Craig[22], Zuzana Diamant[23,24,25], Wojciech Feleszko[26], Tim Felton[1,2], James E Gern[27], Jonathan Grigg[28], Gunilla Hedlin[29], Elham M. Hossny[30], Despo Ierodiakonou[31], Tuomas Jartti[32], Alan Kaplan[33], Robert F. Lemanske[27], Peter Le Souef[34], Mika J Makela[35], Georgios A. Mathioudakis[3], Paolo M. Matricardi[36], Marina Mitrogiorgou [37], Mário Morais-Almeida[38], Karthik Nagaraju[39], Effie Papageorgiou[6], Helena Pite[38,40,41], Paulo MC Pitrez[42], Petr Pohunek[43], Graham Roberts[44,45,46], Ioanna Tsiligianni[31], Stephen Turner[47], Susanne Vijverberg[48], Tonya A. Winders[49,50], Gary Wong[51], Paraskevi Xepapadaki[52], Heather J. Zar[53], Nikolaos G. Papadopoulos[2,52]

* AGM and MM equally contributed to this work.

Affiliations

[1] North West Lung Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK.
[2] Division of Infection, Immunity and Respiratory Medicine, The University of Manchester, Manchester, UK.
[3] Athens Breath Centre, Athens, Greece.
[4] First Department of Pediatrics, University of Athens, "Aghia Sofia" Children's Hospital, Athens, Greece.
[5] Department of Cardiovascular and Thoracic Sciences, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario “A. Gemelli” – IRCCS, Rome, Italy.
[6] Department of Biomedical Sciences, University of West Attica, Athens, Greece.
[7] Department of Paediatrics, Imperial College London, London, UK.
[8] CHU Lille, Université Nord de France, Unité de Pneumologie et Allergologie Pédiatriques, Hôpital Jeanne de Flandre, F-59000 Lille, France.
[9] Departments of Pediatrics and of Social and Preventive Medicine, University of Montreal, Montreal, Canada.
[10] Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, Ankara, Turkey.
[11] Pulmonology and Allergy Unity, University Hospital La Fe, Valencia, Spain.
[12] Children's Hospital Boston, Pediatric Allergy and Immunology, Boston, Massachusetts, USA.
[13] Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK.
[14] Observational and Pragmatic Research Institute, Singapore.
[15] Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK.
[16] Faculty of Medicine, Transylvania University, Brasov, Romania.

[17] Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Washington University, St. Louis, USA.
[18] Institute of Infection and Global Health, University of Liverpool, Liverpool, UK.
[19] National Heart and Lung Institute (NHLI), Imperial College London, UK.
[20] Department of Pediatrics, School of Medicine, Pontifical Universidad Catolica de Chile, Santiago, Chile.
[21] European Federation of Allergy and Airway Diseases Patient's Associations, Brussels, Belgium.
[22] Penn State Allergy, Asthma and Immunology, Hershey, PA, USA.
[23] Department of Respiratory Medicine and Allergology, Institute for Clinical Science, Skane University Hospital, Lund University, Lund, Sweden.
[24] Department of Respiratory Medicine, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic.
[25] Department of Clinical Pharmacy & Pharmacology, University of Groningen, University Medical Center of Groningen and QPS-NL, Groningen, Netherlands.
[26] Department of Pediatric Pulmonology and Allergy, The Medical University Children's Hospital, Warszawa, Poland.
[27] Department of Pediatrics and Medicine, University of Wisconsin School of Medicine and Public Health, Madison, USA.
[28] Centre for Genomics and Child Health, Blizard Institute, Queen Mary University of London, London, UK.
[29] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden.
[30] Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University, Cairo, Egypt.
[31] Health Planning Unit, Department of Social Medicine, Faculty of Medicine, University of Crete, Crete, Greece.
[32] Department of Paediatrics, Turku University Hospital and University of Turku, Turku, Finland.
[33] Family Physician Airways Group of Canada, University of Toronto, Toronto, Ontario, Canada.
[34] School of Paediatrics and Child Health, University of Western Australia, Perth, Australia.
[35] Helsinki University Skin and Allergy Hospital and University of Helsinki, Helsinki, Finland.
[36] Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charité - University Medicine Berlin, Germany.
[37] Third Department of Paediatrics, "ATTIKON" University General Hospital, National and Kapodistrian University of Athens School of Health Sciences, Athens, Greece.
[38] Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal.
[39] VN Allergy & Asthma Research Center, Chennai, Tamilnadu, India
[40] Allergy Center, CUF Infante Santo Hospital, Lisbon, Portugal.
[41] Chronic Diseases Research Center (CEDOC), NOVA Medical School / Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisbon, Portugal.
[42] Laboratory of Respiratory Physiology, Infant Center, School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil.
[43] Paediatric Department, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic.
[44] The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport Isle of Wight, UK.
[45] Faculty of Medicine, Clinical and Experimental Sciences and Human Development in Health Academic Units, University of Southampton, Southampton, UK.
[46] NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK.
[47] Child Health, Royal Aberdeen Children's Hospital and University of Aberdeen, Aberdeen, UK.
[48] Department of Respiratory Medicine and Department of Pediatric Pulmonology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.
[49] Allergy and Asthma Network, Vienna, Virginia, USA.
[50] Global Allergy & Asthma Patient Platform, Vienna, Austria.
[51] Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Sha Tin, Hong Kong.

[52] Allergy Department, 2nd Paediatric Clinic, National and Kapodistrian University of Athens, Athens, Greece.
[53] Department of Paediatrics and Child Health, Red Cross Children's Hospital and SA-Medical Research Council Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa.

Corresponding author:

Professor Nikolaos G. Papadopoulos,

Division of Infection, Immunity & Respiratory Medicine,

The University of Manchester

e-mail: ngpallergy@gmail.com

Phone: +44 161 7016946

Acknowledgement: AGM was supported by the National Institute of Health Research Manchester Biomedical Research Centre (NIHR Manchester BRC). We thank Mrs Maria Kritikou for excellent administrative support of the study.

Abstract

Introduction. Clinical recommendations for childhood asthma are often based on data extrapolated from studies conducted in adults, despite significant differences in mechanisms and response to treatments. The PeARL Think Tank aspires to develop recommendations based on the best available evidence from studies in children. An overview of systematic reviews on pediatric asthma maintenance management and a systematic review of treatments for acute asthma attacks in children, requiring an emergency presentation with/without hospital admission will be conducted.

Methods and analysis. Standard methodology recommended by Cochrane will be followed. Maintenance pharmacotherapy of childhood asthma will be evaluated in an overview of SRs published after 2005 and including clinical trials or real-life studies. For evaluating pharmacotherapy of acute asthma attacks leading to an emergency presentation with/without hospital admission, we opted to conduct de novo synthesis in the absence of adequate up-to-date published SRs. For the SR of acute asthma pharmacotherapy we will consider eligible SRs, clinical trials, or real-life studies without time restrictions. Our evidence updates will be based on broad searches of Pubmed/Medline and the Cochrane Library. We will use AMSTAR-2, Cochrane RoB2 and RELEVANT to evaluate the methodological quality of SRs, controlled clinical trials and real-life studies, respectively.

Next, we will further assess interventions for acute severe asthma attacks with positive clinical results in meta-analyses. We will include both controlled clinical trials and observational studies and will assess their quality using the previously mentioned tools. We will employ random effect models for conducting meta-analyses, and GRADE methodology to assess certainty in the body of evidence.

Ethics and dissemination. Ethics approval is not required for SRs. Our findings will be published in peer reviewed journals and will inform clinical recommendations being developed by the PeARL Think Tank.

Systematic review registration. CRD42020132990, CRD42020171624

Strengths and limitations of this study

- Broad evidence syntheses on the management of childhood asthma, with a focus on the differential treatment response according to age and disease phenotypes could reveal clinically exploitable information, that will be used in the development of clinical and research recommendations by PeARL.
- A rigorous methodology that includes thorough evaluation of the literature, appropriate evaluation of the methodological quality of individual studies and -when appropriate- of the body of evidence, and presentation of overall effect estimates.
- A prospectively published protocol increases the transparency and allowed for peer-review of the methodology utilized.
- A potential limitation of the overview of SRs is that the feasibility of conducting the planned subgroup analyses will depend on whether relevant data have been captured in existing SRs.

Keywords: Asthma, Childhood Asthma, Asthma Maintenance Treatment, Asthma attacks, Asthma attacks in children, Acute Asthma Attacks Treatment, Systematic Reviews, Meta-analyses, Overview of Systematic Reviews.

Introduction

Having a global prevalence that is anticipated to exceed 400 million children by the year 2025, childhood asthma represents a huge health and socioeconomic burden to patients, their families and the society[1,2,3]. Despite its diverging mechanisms, triggers, outcomes and response to treatment, childhood asthma is often still approached as an extension of adult asthma[4]. It is under-addressed in clinical guidelines, likely due to unclear diagnosis, limited availability of safety, efficacy and effectiveness data in this population. Clinical recommendations are to a large extent informed by data extrapolated from clinical studies conducted in adults[2,3,4,5].

Numerous challenges complicate conducting interventional research studies in children with asthma. Besides the lack of consensus on its definition and diagnostic criteria, childhood asthma is highly heterogeneous and our understanding of different pediatric asthma phenotypes is still limited or contradictory[6]. This is further emphasized by significant variability in disease progression, outcomes, and treatment response in children with different phenotypes or ages[5,7], potentially complicating interpretation of trials' findings. In addition, there are regulatory and ethical constraints in conducting interventional research in children[8,9]. However, this results in the administration of treatments that have not been adequately evaluated in relevant (pediatric) populations, that is evidently suboptimal.

Pediatric Asthma in Real Life (PeARL), an international Think Tank focusing on Pediatric Asthma, was initiated in the context of the Respiratory Effectiveness Group (REG), to address this evidence deficit. In a recent international, multi-stakeholder survey, we have identified and prioritised unmet needs on pediatric asthma[10]. A need for systematic evidence updates focusing on the management of asthma in different age groups emerged. Herein, we present the protocol for a series of systematic evidence updates aiming to summarize direct evidence from clinical studies in children with asthma, evaluating the safety and clinical effectiveness of pharmacological interventions for maintenance management and for the treatment of acute severe asthma attacks, defined as those leading to an emergency presentation with/without hospital admission, in different age groups. Our work will be used to inform clinical recommendations being developed by the PeARL Think Tank. Therefore, we need solid evidence on the efficacy on safety of various interventions. It is considered crucial to incorporate evidence derived from real-life observational studies, which may carry a lower strength

of evidence than RCTs, but are available in higher abundance and provide a better representation of clinical practice in real life, where for example, treatment compliance or inhaler technique may be problematic.

Methods and analysis

We will conduct two systematic evidence updates, based on protocols prospectively registered in the PROSPERO register (CRD42020132990[11], CRD42020171624[12]). The first will evaluate the safety and clinical effectiveness of pharmacological maintenance treatments for childhood asthma, while the other will focus on the pharmacotherapy of acute severe asthma attacks, defined as those requiring a hospital admission or emergency presentation. We will use standard methodology recommended by the Cochrane Collaboration[13] and will follow the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14].

Preliminary searches revealed several randomized controlled trials evaluating maintenance pharmacotherapy of childhood asthma, which have already been summarised in high-quality systematic reviews (SRs), some conducted by the Cochrane Collaboration. We identified >40 up-to-date SRs evaluating inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA) or biologic therapies, as first line or add-on treatment for asthma in children. As a result, we opted to produce an overview of existing SRs of clinical trials and real-life studies[15].

We found less up-to-date SRs on the management of acute severe asthma attacks in children, mainly focusing on short-acting beta-2 agonists (SABA), short acting muscarinic antagonists (SAMA), oral corticosteroids, aminophylline and magnesium, that were recently summarized in a Cochrane Overview of SRs[16]. However, when evaluating the literature, we identified several other pharmacological interventions that are tested in small trials or real-life studies, and while they may show promising early results, they have not been assessed further or introduced in clinical practice guidelines[17,18,19,20,21,22,23]. For this reason, we will conduct de novo synthesis of comparative clinical studies of any design aiming to identify any pharmacological intervention that has been tested for acute severe asthma attacks, followed by focused meta-analyses of promising interventions not covered by existing high-quality SRs or clinical practice guidelines.

a. **Overview of SRs evaluating maintenance pharmacotherapy for pediatric asthma.**

Eligibility criteria

Eligible studies will comprise SRs and meta-analyses of controlled clinical trials or of real-life studies evaluating maintenance treatments that are broadly used in clinical practice for asthma or recurrent wheeze in children and adolescents, aged up to 18 years. More specifically, we will include SRs comparing any combination of ICS, LABA, LAMA, LTRA, biologic therapies (namely omalizumab, mepolizumab, reslizumab, benralizumab or dupilumab), or placebo as monotherapy or add-on maintenance therapy for pediatric asthma. We will accept SRs and meta-analyses evaluating any molecule of the above-mentioned categories, administered at any dose and for a duration of at least six weeks. SRs comparing asthma maintenance treatment both in children and adults will be included provided that pediatric data are presented separately. We will only include SRs published between 2005 and December 2020 and reported in the English language. Older SRs are probably outdated and will only be considered in the absence of high-quality, newer SRs.

Outcome measures

The primary outcomes of this overview will be the number of acute attacks requiring the administration of oral corticosteroids or an emergency visit, and the number of acute attacks requiring hospitalization. Secondary outcomes will include lung function measures, acute attacks irrespective of the severity, symptom scores (including symptom free and rescue medication free days), asthma control, asthma-specific quality of life scores, use of rescue medications, withdrawal rates (overall, due to lack of efficacy, or adverse events), adverse events and serious adverse events.

Search strategy and study selection

The electronic databases of Medline/PubMed and Cochrane Library will be systematically searched, using appropriate controlled vocabulary and free search terms to identify relevant SRs (terms describing: childhood asthma, LABA, LAMA, LTRA, ICS, biologics, SRs, detailed search strategy is available in the online appendix). Databases will be searched from 2006 onwards. Titles and abstracts of all identified manuscripts, and the full texts of potentially relevant manuscripts, will be screened by two investigators independently. We will report

the reasons of exclusion of studies that will be excluded after full-text review. Disagreement will be resolved through discussion or adjudication by a third investigator, when necessary.

Data abstraction

For each of the included SRs, one investigator will extract the full reference and study identifiers, references of the included trials evaluating pediatric populations, eligibility criteria, predefined outcomes, number and baseline characteristics of the participants and details on the outcomes of interest. A second investigator will cross-check for validity.

Risk of Bias Assessment

AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews, version 2) tool will be used to evaluate the methodological quality of all included SRs[24,25]. The AMSTAR 2 tool evaluates 16 domains, focusing on the methodological design, interpretation and potential risk of bias involved in the conduct of a SR. It is considered by the AMSTAR 2 team that seven domains could critically affect the validity of the review, while the remaining domains describe non-critical weaknesses. Critical flaws for a SR include (i) lack of prospective protocol registration, (ii) inadequate literature searches, (iii) lack of justification of excluding individual studies, (iv) of risk of bias evaluation or (v) of risk of bias consideration in interpreting the results, (vi) of assessment of presence and likely impact of publication bias and (vii) inadequate methodology for conducting meta-analysis. We will consider the results of a SR of high quality, if there is only one or none non-critical weakness, and of moderate quality, if there are more than one non-critical weaknesses. If there are one or more critical weaknesses, then we will consider the confidence low or very low, respectively. Two of the systematic reviewers will evaluate the risk of bias independently and disagreement will be resolved through discussion, or adjudication by a third reviewer.

Qualitative synthesis

We will summarise descriptively or in a tabulated format the characteristics of the included SRs and outcomes of interest. When several SRs evaluate the same intervention, we will compare their eligibility criteria, included studies, and methodological quality as evaluated by the AMSTAR-2 tool, as well as the pertinent subgroup analyses that are presented. We will present in detail the results of the SR that is most recent, more complete

and of high methodological quality. If no single SR fulfil these criteria, we will present in detail more than one SRs. From the remaining SRs, we will present pertinent additional information that may include, such as details about additional outcomes, or additional subgroups.

We will specifically report on the differential effectiveness of the interventions across different maintenance treatment steps (severity), age groups or pediatric asthma phenotypes.

b. **SR of clinical studies evaluating the management of acute severe asthma attacks.**

Over the past decades, several interventions have been tested for the management of acute severe asthma attacks, such as ketamine or macrolide antibiotics[17,18,19,20,21,22,23]. Despite promising early findings, some of these interventions were not further tested in robust, prospective controlled clinical trials. This may partially be due to challenges in conducting experimental clinical studies in children, as previously discussed, particularly during acute, life-threatening conditions.

To identify all evaluated treatments, a two-stage approach will be followed. Firstly, a broad search strategy will be used to identify all pharmacological interventions that have been tested as potential treatments for acute severe asthma attacks. Next, medications that showed positive clinical results, but are not yet thoroughly evaluated in clinical studies and meta-analyses and are therefore not recommended by international asthma guidelines (such as the National Institute for Health and Care Excellence [NICE] asthma guidelines, the British Thoracic Society and Scottish Intercollegiate Guidelines Network [BTS/SIGN] asthma guidelines, the National Asthma Education and Prevention Program [NAEPP], or the Global Strategy for Asthma Management and Prevention [GINA] document), will be selected and further evaluated in individual meta-analyses. The aim will be to identify novel interventions that could be recommended for use in clinical practice, or might require further evaluation in clinical research studies, to confirm their safety and effectiveness profiles.

Broad SR

Medline/PubMed and the Cochrane Library will be searched, using a broad search strategy, aimed to identify any clinical research studies evaluating the management of acute severe asthma attacks (detailed search strategy is available in the online appendix).

Any study evaluating pharmacological treatments for acute severe asthma attacks in children and adolescents (< 18 years of age) will be included. Any comparative clinical research study, including experimental and observational studies, as well as SRs of such studies will be considered eligible for inclusion. We will only include studies published until May 2021 and reported in the English language, without time restrictions.

Eligible studies will be grouped according to the drug category they evaluate and will be presented narratively. Study design, characteristics and outcomes of interest will be reported descriptively or in a tabulated format. Outcomes of interest are the same for this broad SR and individual medication meta-analyses and are detailed in the next section.

Individual medication meta-analyses

These meta-analyses will further evaluate the safety and clinical effectiveness of individual medications that were assessed by the initial broad SR and were found to be of potential clinical value for the treatment of acute severe asthma attacks. In contrast to most preceding SRs and meta-analyses, we will include data from observational comparative effectiveness (real-life) studies, as well as controlled clinical trials.

Eligibility criteria

For each meta-analysis, eligible studies will comprise controlled clinical trials and observational comparative effectiveness studies comparing the index medication with placebo, no treatment or any active control, as an add-on treatment for acute severe asthma attacks. Index medication will be defined based on the pharmacological action, meaning that molecules targeting the same pharmacological target (e.g. salbutamol and terbutaline, both being short-acting beta-2 agonists) will be grouped. Only studies evaluating the management of acute severe asthma attacks, defined as those requiring a hospital admission or emergency presentation, in children and adolescents, aged between 1 and 18 years of age will be included. Studies evaluating both children and adults will be included, provided that pediatric data are reported separately or

that we will be able to access these data after requesting them from the investigators. We will only include observational studies that meet the primary criteria of the RELEVANT tool (see risk of bias). We will include studies published until May 2021 and reported in the English language.

Outcome measures

The primary outcome measures will be (i) treatment success or treatment failure rate evaluated at any timepoint, within 2 weeks from presentation, (ii) serious adverse events and, (iii) need for asthma related hospitalization evaluated at any timepoint within 2 weeks from presentation. Treatment success will be defined as a complete resolution of the symptoms, or an improvement in the clinical signs, symptoms and/or laboratory findings that fulfils specific criteria or thresholds prespecified by the study team. Treatment failure will be defined as a significant deterioration of the patients' clinical conditions that fulfils specific criteria prespecified by the study team. For example, treatment failure may be defined as the need for paediatric intensive care unit admission, ventilation, or death. The definitions of treatment success and treatment failure vary significantly across clinical studies evaluating the management of acute asthma in children; for this reason, meta-analyses will only be conducted in cases they are considered meaningful by the investigators. Need for asthma related hospitalization will not be relevant for studies only evaluating hospitalized participants. Secondary outcomes will include (i) mortality, (ii) duration of asthma-related hospitalization, (iii) need for intensive care unit admission, (iv) duration of intensive care unit stay, (v) re-exacerbation rate, (vi) re-hospitalization rate, (vii) adverse events. All outcomes will be evaluated at a maximum follow-up of 6 months, as longer-term outcomes are less likely to be directly linked with the index acute event.

Search strategy and study selection

Using appropriate controlled vocabulary and free search terms, we will systematically search Medline/ Pubmed, EMBASE and the Cochrane Library to identify controlled clinical trials and observational comparative effectiveness studies evaluating the safety, efficacy and/or clinical effectiveness of the selected medication (sample search strategies are available in the online appendix). We will also search the World Health Organization International Clinical Trials Registry Platform (ICTRP) search portal, the abstract proceedings of the European Respiratory Society, the American Thoracic Society, the Asian Pacific Society of Respirology, the European Academy of Allergy and Clinical Immunology, the American Academy of Allergy, Asthma and

Immunology, and the World Allergy Organization, as well as the reference lists of all included studies. All sources will be searched from inception, without language limitations. We will follow standard methodology for screening titles, abstracts and the full text of all identified studies, as described previously.

Data abstraction

The full study reference, study identifiers, details on the study design, eligibility criteria, predefined outcomes and potential confounding factors that were considered by the investigators, number and baseline characteristics of participants will be extracted by one investigator and will be cross-checked for validity by a second extractor. Details on the outcomes of interest from all included studies will be extracted by two investigators independently. Conflicts will be resolved through discussion and when needed adjudication by a third investigator.

Risk of bias of individual studies

We will use the second version of the Cochrane risk of bias (RoB2) tool for assessing risk of bias in the included RCTs[26] and the REal Life EVidence AssessmeNt Tool (RELEVANT) for assessing the risk of bias of observational studies[27]. Risk of bias of each included study will be evaluated by two investigators independently.

The RoB2 tool evaluates the following domains for potential risk of bias: (i) bias arising from the randomization process, (ii) bias due to deviations from intended interventions, (iii) bias due to missing outcome data, (iv) bias in measurement of the outcome, (v) bias in selection of reported results and (vi) any other potential source of bias. High risk of bias in any of these domains will result in an overall judgement of high risk of bias. In the absence of high-risk domains, unclear risk in any domain will lead to an overall judgement of unclear risk. All remaining trials will be considered to be of low risk of bias.

RELEVANT evaluates the quality of observational comparative effectiveness research studies across seven domains, which include background, design, measures, analysis, results, discussion/interpretation and conflicts of interest. Each domain includes primary and secondary items. It is suggested that studies not meeting the primary items of RELEVANT are of very low methodological quality (have “fatal flaws”) and should not be used to inform clinical recommendations. Therefore, we will exclude studies not meeting these criteria.

We will consider of low risk of bias all studies meeting the secondary criteria of RELEVANT as well, and of high risk of bias studies that do not meet any of the secondary criteria.

For every comparison, we will use funnel plots, Egger's regression and Begg's rank tests to evaluate publication bias, if we are able to pool more than 10 studies.

Data synthesis

Data from controlled clinical trials or observational studies will be analysed separately. In addition, studies evaluating different comparators, will be analysed separately. If different doses of the index medication or comparator are evaluated across the included studies, we will consider grouping studies using similar doses, providing that their results are not significantly dissimilar.

For every analysis, I^2 statistic will be used to assess statistical heterogeneity. Substantial heterogeneity (I^2> 50%) will be explored using prespecified subgroup analyses (details in the next section). We will not perform meta-analyses in cases of considerable unresolved heterogeneity (I^2 >75%).

When it is considered meaningful, meta-analyses will be performed using the random-effects model, because we anticipate significant heterogeneity in our data. Results will be presented in the form of relative risk (RR, 95% confidence intervals – CI) for dichotomous data, mean difference (MD, 95% CI) for continuous data and hazard ratios (HR, 95% CI) for time to event data. Meta-analyses will be performed using Review Manager version 5 (RevMan, http://community.cochrane.org/tools/review-production-tools/revman-5) and R statistics version 3.4.3 or newer (R Foundation for Statistical Computing, Vienna, Austria).

For dichotomous outcomes, the unit of analysis will preferably be participants, rather than events (i.e. number of participants admitted to the intensive care unit, rather than number of admissions per participants).

Sensitivity and subgroup analyses

In sensitivity analyses for all comparisons, we will (i) use fixed effects models, (ii) only include studies with low risk of bias, (iii) exclude studies reporting limited adherence to the study drugs (<80%), and (iv) evaluate separately studies assessing different doses of the index medication, which we may pool in the main analysis.

Subgroup analyses according to participants' age, asthma phenotypes or, possibly, acute attack phenotypes will also by conducted, depending on data availability. In an additional subgroup analysis, we will evaluate separately trials utilising exploratory versus pragmatic study designs.

Certainty of the body of evidence

Certainty of the body of evidence, for every comparison will be evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology[28]. GRADE assesses the certainty in a body of evidence as high, moderate, low, or very low after considering the methodological quality of the included studies, imprecision, inconsistency, indirectness, publication bias, the magnitude of effect, dose response, and confounders likely to minimize the effect. All decisions to upgrade or downgrade the quality of evidence will be transparent and justified in evidence profile and summary of evidence tables, in accordance with GRADE guidance. GRADEPro Software (2014; www.gradepro.org) will be used for the development of these tables.

We will use GRADE methodology to assess the risk of bias associated with missing participant outcome data across the body of the available evidence[29]. GRADE suggests repeating the primary meta-analysis, imputing the most extreme assumptions about the values of the missing data, that the investigators consider plausible. Only if the analyses prove robust to this imputation, the risk of bias due to missing participant outcome data should be deemed low.

The impact that the risk of bias of individual studies and the confidence in the body of the evidence has on the results will be presented.

Ethics and dissemination

Ethical approval is not required for these SRs, since no primary data will be collected.

The findings of these evidence updates will be presented in national and international scientific conferences. They will also be submitted for publication in high-impact peer review journals. Plain English summaries of the final reports will be developed and shared with relevant patient organisations. Moreover, our results will be

used to inform clinical recommendations that will be developed by the PeARL Think Tank. We anticipate that the overview of SRs will be completed by the end of 2021 and the remaining SRs by June 2022.

Patient and public involvement

The planned systematic reviews were prioritized through a global, multi-stakeholder survey evaluating research priorities in childhood asthma, conducted by the PeARL think tank[10]. Among other stakeholders, this survey included responses from patients, patient caregivers and patient organizations. Moreover, two patient representatives (GDC, TAW) have joined the research group and provided input in this study protocol and they will also provide input throughout the study process.

Discussion

We report on the methodology of a series of planned systematic evidence updates, aiming to evaluate maintenance management of childhood asthma, and the treatment of acute severe asthma attacks. Their design is informed by preliminary searches and the anticipated data availability. These SRs will be conducted by the PeARL group and will be used to inform clinical recommendations and future research needs. The need for high-quality evidence updates and clinical practice guidelines to improve the management of asthma in children is more urgent now, given the pressure that the unfolding coronavirus disease 19 (COVID-19) pandemic pose on the health care systems, forcing us to reconsider our daily clinical practice[30,31].

Major strengths of our evidence update series are the inclusion of a wide evidence base, including data from RCTs and real-life comparative studies, the prospective design and strong methodology. The methodological quality of all available studies will be scrutinized and will aid the interpretation of our findings. Moreover, we will attempt to evaluate differential therapeutic response of different asthma phenotypes and age groups. We believe this analysis will be revealing, if adequate data is available, but may nevertheless reveal important gaps.

Guided by the available evidence, we will follow different strategies for the evidence updates on maintenance treatment of pediatric asthma and on management of acute severe asthma attacks. In view of the availability

of ample published, up-to-date SRs on maintenance pharmacotherapy of childhood asthma, we chose to conduct an overview of SRs. We decided to focus on the most frequently used and thoroughly evaluated drug classes (ICS, LABA, LAMA, LTRA, and biologic therapies) and we expect to identify good quality data, which would inform clinical practice and research needs. Other, less frequently or experimentally used treatments will need to be evaluated in future studies. A potential limitation of this approach is that we might not be able to capture adequate data regarding the differential effectiveness of interventions across different severity groups, age groups, or pediatric asthma phenotypes, if these have not been captured in existing SRs. Moreover, existing SRs may not capture some of the most recent studies, that may have been published after the SRs, although preliminary searches have revealed several very recently update meta-analyses.

The second SR, focusing on the management of acute attacks, will first evaluate a multitude of established and experimental treatments. With regards to the latter, this SR will reveal treatments that have been tested, appeared safe and efficacious and it may be worth to be further evaluated, but will also report on interventions that were tested, but did not appear efficacious, and therefore, further evaluation may not be beneficial. This wide approach would aid the prioritisation of interventions to be further validated in future clinical research studies.

Next, meta-analyses of individual pharmacological interventions will be conducted to further assess the safety and clinical effectiveness of treatments for acute severe asthma attacks that will appear efficacious in our broad SR. In contrast to most previous meta-analyses, that may have been conducted, we will include both controlled clinical trials and observational comparative effectiveness studies. Due to limitations that have already been discussed, few controlled clinical trials are conducted in children. This leads several Cochrane SRs to report low or very low confidence in the body of evidence, due to the lack of data[32,33,34,35]. We believe that by incorporating data from observational studies we may be able to conclude more robust results. While observational studies are at a higher risk of bias, we will carefully evaluate this risk using the newly developed, thorough RELEVANT tool and we will discuss potential implications on our findings. The GRADE working groups provides transparent guidance for assessing the certainty in a body of evidence including data from different study designs (controlled clinical trials or observational studies); this guidance will be used for interpreting the findings of our meta-analyes.

Overall, we aim to develop evidence updates on the maintenance treatment of asthma and management of acute severe asthma attacks, that will cover all available evidence, carefully considering methodological limitations. These will be used by the PeARL Think Tank for the development of clinical recommendations and to guide future clinical research.

Author contribution: Study conception: AGM, NGP. Study design: AGM, MM, NGP. Preparation of the manuscript: AGM. Critical revision and final approval of the manuscript: AGM, MM, CB, GSA, AC, AD, FMD, OK, CM, ANG, WP, DP, AS, IA, LB, AB, AB, MB, JACR, GDC, TC, ZD, WF, TF, JEG, JG, GH, EMH, DI, TJ, AK, RFL, PLS, MJM, GAM, PMM, MM, MMA, KN, EP, HP, PMCP, PP, GR, IT, ST, SV, TAW, GW, PX, HJZ, NGP

Declaration of Interests: *This study was supported by the Respiratory Effectiveness Group (REG). None of the authors had any conflicts of interest directly related to this work. MM, GSA, IA, AB, AB, AB, MB, GDC JACR, WF, GC, GH, EMH, DI, TJ, OK, MJM, GAM, PMM, MM, MM-A, KN, EP, ANG, HP, PMCP, SS-G PLS, AS, ST, SV, TW, GW, HZ do not declare any conflicts of interest outside the submitted work either. AGM reports grants from Boehringer Ingelheim outside the submitted work. AC reports personal fees from Novartis, Regeneron / Sanofi, Thermo Fisher Scientific, Boehringer Ingelheim and Philips, outside the submitted work. LB reports personal fees from Aerocrine, GlaxoSmithKline, Genentech/Novartis, Merck, DBV Technologies, Teva, Boehringer Ingelheim, AstraZeneca, WebMD/Medscape, Sanofi/Regeneron, Vectura and Circassia outside the submitted work. TC reports grants and personal fees CSL Behring, Dyax, Takeda, BioCryst, Pharming, personal fees from Grifols, grants and non-financial support from GSK, Regeneron, Novartis/Genetech outside the submitted work. AD reports grants and personal fees from Stallergenes Greer, personal fees from Novartis, ALK, TEVA, GSK, MEDA-MYLAN, CHIESI, AImmune, DBV technologies and Astra Zeneca, outside the submitted work. ZD reports personal fees from academic affiliations, ZD acts as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies. ZD reports personal fees from Astrazeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD, and Sanofi-Genzyme outside the submitted work. FMD reports grants from Thorasys Inc; personal fees from Jean-Coutu Pharmaceuticals, unrestricted research funds from Novartis Canada, Teva and Trudell Medical, research grants* from GlaxoSmithKline and MEDteq in partnership with Thorasys Inc.; honorarium for consultancy work from Covis Pharma and Teva; and honorarium as invited speaker from Covis Pharma, Pharmacy Brunet, *outside the submitted work. JEG reports grants from NIH/NIAID, personal fees from Regeneron, Ena Theraputics and MedImmune outside the submitted work; personal fees and stock options from Meissa Vaccines Inc outside the submitted work. JG reports personal fees from GSK, Vifor Pharmaceuticals, Novartis, BV Pharma and AstraZeneca outside the submitted work. AK reports personal fees Astra Zeneca, Behring, Boehringer Ingelheim, Covis, GSK, NovoNordisk, Novartis, Griffols, Pfizer, Sanofi, Teva and Trudel, outside the submitted work. RFL reports grants from NIH, non-financial support from GlaxoSmithKline, Boehringer-Ingelheim, Merck, TEVA, American Academy of Allergy, Asthma and Immunology, grants from Clinical and Translational Science Award (NIH), Childhood Origins of ASThma (COAST) grant , AsthmaNet, personal fees from LSU, Elsevier, UpToDate, the University of Kentucky, ThermoFischer, and Food Allergy Research and Education (FARE) Network, outside the submitted work. CM reports personal fees from Novartis, GSK, Astra Zeneca, Thermo Fisher and Boehringer Ingelheim outside the submitted work. NGP reports personal fees from ALK, Novartis, Nutricia, HAL, Menarini/FAES Farma, Sanofi, Mylan/MEDA, Biomay, AstraZeneca, GSK, MSD, ASIT BIOTECH and Boehringer Ingelheim; grants from Gerolymatos International SA and Capricare outside the submitted work. WP reports grants from NIH; grants and personal fees from Genentech/Novartis, Sanofi/Rgeneron; personal fees GSK; non-financial support from Thermo Fisher, Lincoln Diagnostics, Alk Abello, and Monaghen, outside the submitted work. PP reports grants from Astra Zeneca, Chiesi and TEVA; personal fees from Astra Zeneca, TEVA, Novartis, Mundipharma, S&D Pharma, and GlaxoSmithKline outside the submitted work. DP reports grants from AKL Research and Development Ltd, British Lung Foundation, Respiratory Effectiveness Group and the UK National Health Service; grants and personal fees from Boehringer*

Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, TEVA, Theravance, and Zentiva (Sanofi Generics); personal fees from Cipla, GlaxoSmithKline, Kyorin, and Merck; non-financial support from Efficacy and Mechanism Evaluation programme, Health Technology Assessment, outside the submitted work; DP also reports stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; and owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore), outside the submitted work. GCR reports personal fees from ALK, Allergen Therapeutics, Meda Plus, Merck; and a patent for the use of sublingual immunotherapy to prevent the development of allergy in at-risk infants, outside the submitted work. IT reports personal fees from Novartis, GSK, Boehringer Ingelheim, and Astra Zeneca; grants from GSK Hellas, outside the submitted work. PX reports personal fees from Nutricia, Nestle, Friesland, Uriach, Novartis Pharma AG, and GlaxoSmithkline outside the submitted work.

Funding: This work was supported by the Respiratory Effectiveness Group (REG). REG has received support from AstraZeneca, Novartis and Sanofi for continued work on PeARL. (Award/Grant name: PeARL, Award/Grant Number: N/A). This is an investigator initiated study and the funders were not involved in the selection of the topic, or design of these systematic reviews.

References:

[1] To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12: 204. https://doi.org/10.1186/1471-2458-12-204.

[2] Global Initiative for Asthma. GINA guidelines. Global strategy for Asthma Management and Prevention. Available at: www.ginasthma.org (accessed March 1, 2018).

[3] British Thoracic Society, Scottish Intercollegiate Guidelines Network. SIGN 158: British guideline on the management of asthma. BTS/SIGN, Edinburgh, 2019.

[4] Papadopoulos NG, Čustović A, Cabana MD, Dell SD, Deschildre A, Hedlin G, et al. Pediatric asthma: An unmet need for more effective, focused treatments. Pediatr Allergy Immunol. 2019 Feb;30(1):7-16. doi: 10.1111/pai.12990.

[5] Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R, et al. International consensus on (ICON) pediatric asthma. Allergy. 2012 Aug;67(8):976-97.

[6] Kwong CG, Bacharier LB. Phenotypes of wheezing and asthma in preschool children. Curr Opin Allergy Clin Immunol. 2019 Apr;19(2):148-153.

[7] Tse SM, Krajinovic M, Chauhan BF, Zemek R, Gravel J, Chalut D, et al. Genetic determinants of acute asthma therapy response in children with moderate-to-severe asthma exacerbations. Pediatr Pulmonol. 2019;54(4):378-385.

[8] Multidisciplinary scientific guidelines: paediatrics http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000404.jsp&mid=WC0b01ac0580029572 (2013).

[9] Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Global Research in Paediatrics. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014 Jun;73:2-13.

[10] Mathioudakis AG, Custovic A, Deschildre A, Ducharme FM, Kalayci O, Murray C, et al. Research priorities in pediatric asthma: Results of a global survey of multiple stakeholder groups by the Pediatric Asthma in Real Life (PeARL) Think Tank. *J Allergy Clin Immunol Pract 2020. In Press.*

[11] Mathioudakis AG, Miligkos M, Papadopoulos NG. Maintenance treatment for childhood asthma: A protocol for an overview of systematic reviews by the PeARL think-tank. International prospective register of systematic reviews (PROSPERO). 2020. CRD42020132990

[12] Mathioudakis AG, Alimani GS, Papadopoulos NG. Pharmacological management of acute severe asthma attacks in children. Protocol for a systematic review by the PeARL think tank. International prospective register of systematic reviews (PROSPERO). 2020. CRD42020171624.

[13] Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. 2011.

[14] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-12.
[15] Thomson D, Russell K, Becker L, Klassen T, Hartling L. The evolution of a new publication type: steps and challenges of producing overviews of reviews. Research Synthesis Methods 2010; 1: 13.
[16] Craig SS, Dalziel SR, Powell CV, Graudins A, Babl FE, Lunny C. Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2020 Aug 5;8:CD012977. doi: 10.1002/14651858.CD012977.pub2.
[17] Katsunuma T, Fujisawa T, Maekawa T, Akashi K, Ohya Y, Adachi Y, et al. Low-dose L-Isoproterenol Versus Salbutamol in Hospitalized Pediatric Patients With Severe Acute Exacerbation of Asthma: A Double-Blind, Randomized Controlled Trial. Allergol Int. 2019; 68(3), 335-341.
[18] Alshehri M, Almegamesi T, Alfrayh A. Efficacy of nebulized furosemide in children with moderate attack of asthma. West Afr J Med. 2005 Jul-Sep;24(3):246-51.
[19] Douglas LC, Choi J, Esteban-Cruciani N. Azithromycin treatment in children hospitalized with asthma: a retrospective cohort study. J Asthma. 2020 May;57(5):525-531. doi: 10.1080/02770903.2019.1590590. Epub 2019 Apr 1. PMID: 30929521.
[20] Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. Ann Emerg Med. 2005 Jul;46(1):43-50.
[21] Mathioudakis A, Chatzimavridou-Grigoriadou V, Evangelopoulou E, Mathioudakis G. Vasoactive intestinal Peptide inhaled agonists: potential role in respiratory therapeutics. Hippokratia. 2013 Jan;17(1):12-6.
[22] Robroeks CM, van de Kant KD, van Vliet D, Kester AD, Hendriks HJ, Damoiseaux JG, Wodzig WK, Rijkers GT, Dompeling E, Jöbsis Q. Comparison of the anti-inflammatory effects of extra-fine hydrofluoroalkane-beclomethasone vs fluticasone dry powder inhaler on exhaled inflammatory markers in childhood asthma. Ann Allergy Asthma Immunol. 2008 Jun;100(6):601-7.
[23] Tantichaiyakul P, Preutthipan A. Ketotifen versus inhaled budesonide for controlling childhood asthma. J Med Assoc Thai. 2010 May;93(5):541-9.
[24] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008.
[25] Pollock M, Fernandes R, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions. BMC Medical Research Methodology 2017b; 17: 13.
[26] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.
[27] Campbell JD, Perry R, Papadopoulos NG, Krishnan J, Brusselle G, Chisholm A, et al. The REal Life EVidence AssessmeNt Tool (RELEVANT): development of a novel quality assurance asset to rate observational comparative effectiveness research studies. Clin Transl Allergy. 2019 Mar 27;9:21.
[28] Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6.
[29] Guyatt GH, Ebrahim S, Alonso-Coello P, Johnston BC, Mathioudakis AG, Briel M, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. J Clin Epidemiol. 2017 Jul;87:14-22.
[30] Papadopoulos NG, Custovic A, Deschildre A, Mathioudakis AG, Phipatanakul W, Wong G, et al. Impact of COVID-19 on Pediatric Asthma: Practice Adjustments and Disease Burden. J Allergy Clin Immunol Pract. 2020 Sep;8(8):2592-2599.e3. doi: 10.1016/j.jaip.2020.06.001.
[31] Papadopoulos NG, Mathioudakis AG, Custovic A, Deschildre A, Phipatanakul W, Wong G, et al. Childhood asthma during the COVID-19 pandemic: Findings from the PeARL multi-national cohort. Allergy. 2021:10.1111/all.14787.
[32] Vézina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. Cochrane Database Syst Rev. 2014 Jul 31;(7):CD010283.
[33] Normansell R, Kew KM, Mathioudakis AG. Interventions to improve inhaler technique for people with asthma. Cochrane Database Syst Rev. 2017 Mar 13;3:CD012286.
[34] Normansell R, Kew K, Stovold E, Mathioudakis AG, Dennett E. Interventions to improve inhaler technique and adherence to inhaled corticosteroids in children with asthma. Paediatr Respir Rev. 2017 Jun;23:53-55.
[35] Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2017 Nov 28;11:CD003898.

Online Appendix

Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.

Search Strategies

1. Overview of SRs evaluating stable asthma treatment

#1 Asthma [MH]

#2 Respiratory Sounds[MH]

#3 Bronchial spasm [MH]

#4 Bronchial Hyperreactivity [MH]

#5 Respiratory Hypersensitivity [MH]

#6 Anti-asthmatic agents[MH]

#7 Asthma [tiab]

#8 Wheez* [tiab]

#9 Bronchospas* [tiab]

#10 Bronchoconstrict* [tiab]

#11 Bronch* [tiab] and (constrict* [tiab])

#12 (bronchial* [tiab] or (respiratory[tiab]) or (airway* [tiab]) or (lung* [tiab])) and (hypersensitiv* [tiab] or (hyperreactiv* [tiab]) or (allerg* [tiab]))

#13 OR / 1-12

#14 (Steroid* [tiab] or (corticosteroid* [tiab]) or (glucocorticoid* [tiab])) and (inhal* [tiab])

#15 Beclomethasone [MH]

#16 Budesonide [MH]

#17 Fluticasone [MH]

#18 Mometasone Furoate [MH]

#19 Triamcinolone [MH]

#20 Beclomethasone [tiab]

#21 Beclometasone [tiab]

#22 Budesonide [tiab]

#23 Fluticasone [tiab]

#24 Ciclesonide [tiab]

#25 Mometasone [tiab]

#26 Flunisolide [tiab]

#27 Triamcinolone [tiab]

#28 ICS [tiab]

#29 OR/ 14-28

#30 Adrenergic beta-2 receptor Agonists [MH] and (inhal* [tiab])

#31 Beta-agonist* [tiab] and (inhal* [tiab])

#32 Salmeterol Xinafoate [MH]

#33 Formoterol Fumarate [MH]

#34 Clenbuterol [MH]

#35 Salmeterol [tiab]

#36 Formoterol [tiab]

#37 Vilanterol [tiab]

#38 Indacaterol [tiab]

#39 Clenbuterol [tiab]

#40 Olodaterol [tiab]

#41 Bambuterol [tiab]

#42 *formoterol [tiab]

#43 LABA [tiab]

#44 OR/ 30-43

#45 Muscarinic antagonists [MH] and (inhal* [tiab])

#46 Tiotropium Bromide [MH]

#47 Tiotropium [tiab]

#48 Umeclidinium [tiab]

#49 GSK573719 [tiab]

#50 Aclidinium [tiab]

#51 LAS34273 [tiab]

#52 Glycopyrronium [tiab]

#53 NVA237 [tiab]

#54 LAMA [tiab]

#55 Muscarinic* [tiab] and (Antagonist* [tiab]) and (inhal* [tiab])

#56 Antimuscarinic* [tiab]

#57 OR/ 45-56

#58 Leukotriene Antagonists[MH]

#59 Leukotriene* [tiab] AND (Antagonist* [tiab])

#60 Anti-leukotriene* [tiab]

#61 Anti-leucotriene [tiab]

#62 Montelukast [tiab]

#63 Zafirlukast [tiab]

#64 Pranlukast [tiab]

#65 LTRA [tiab]

#66 OR/ 58-65

#67 Biological Factors [MH]

#68 Omalizumab [MH]

#69 Omalizumab [tiab]

#70 Mepolizumab [tiab]

#71 Benralizumab [tiab]

#72 Reslizumab [tiab]

#73 Dupilumab [tiab]

#74 OR/ 67-73

#75 meta-analysis [Publication type] *HIRU Filter for Systematic Reviews*

#76 meta-analysis [MH]

#77 meta-analysis [tiab]

#78 review [Publication type]

#79 search*[tiab]

#80 OR/ 75-79

#81 #28 OR #44 OR #57 OR #66 OR #74

#82 #13 AND #80 AND #81

#83 children [MH] or (adolescents [MH])

#84 adults [MH] NOT #75

#85 Editorial [publication type]

#86 Letter [publication type]

#87 #82 NOT (#84 OR #85 OR #86)

2. Severe asthma exacerbations treatment: Broad systematic review

#1 Asthma [MH]

#2 Severe asthma [MH]

#3 Brittle asthma [MH]

#4 Asthma [tiab]

#5 OR/ 1-4

#6 Disease Exacerbation [MH]

#7 Exacerbation [tiab]

#8 Exacerbation* [tiab]

#9 Attack [tiab]

#10 Acute [tiab]

#11 OR/ 6-10

#12 Intensive care [MH]

#13 Emergency Service, Hospital[MH]

#14 Severe [tiab]

#15 Refractory [tiab]

#16 Near fatal [tiab]

#17 Life-threatening [tiab]

#18 Difficult-to-treat [tiab]

#19 Therapy resistant [tiab]

#20 Intensive care[tiab]

#21 Critically ill [tiab]

#22 ICU [tiab]

#23 Emergency presentation [tiab]

#24 Emergency admission [tiab]

#25 Emergency department [tiab]

#26 OR/ 12-25

#27 (#5 AND #11 AND #26)

#28 Status asthmaticus[MH]

#29 Status asthmaticus[tiab]

#30 (#27 OR #28 OR #29)

#31 (animals [mh] NOT humans [mh])

#32 children [MH] or (adolescents [MH])

#33 adults [MH] NOT #32

#34 Review [publication type]

#35 Systematic review [publication type]

#36 Meta-analysis[publication type]

#37 (#34 NOT (#35 or #36))

#38 Letter [publication type]

#39 Editorial [publication type]

#40 (#30 NOT (#31 OR #33 OR #37 OR #38 OR #39))

3. Severe asthma exacerbations treatment: Individual medication meta-analyses

#1 Asthma [MH]

#2 Respiratory Sounds[MH]

#3 Bronchial spasm [MH]

#4 Bronchial Hyperreactivity [MH]

#5 Respiratory Hypersensitivity [MH]

#6 Anti-asthmatic agents[MH]

#7 Asthma [tiab]

#8 Wheez* [tiab]

#9 Bronchospas* [tiab]

#10 Bronchoconstrict* [tiab]

#11 Bronch* [tiab] and (constrict* [tiab])

#12 (bronchial* [tiab] or (respiratory[tiab]) or (airway* [tiab]) or (lung* [tiab])) and (hypersensitiv* [tiab] or (hyperreactiv* [tiab]) or (allerg* [tiab]))

#13 OR / 1-12

#14 Search terms related to the medication under investigation, including MeSH terms and free search terms.

#15 children [MH]

#16 paediatric*[tiab]

#17 pediatric* [tiab]

#18 child* [tiab]

#19 adolescen* [tiab]

#20 infant* [tiab]

#21 toddler* [tiab]

#22 preschool* [tiab]

#23 OR/ 16-22

#24 #13 AND #14 AND #23

#25 (animals [mh] NOT humans [mh])

#26 children [MH] or (adolescents [MH])

#27 adults [MH] NOT #26

#28 Review [publication type]

#29 Systematic review [publication type]

#30 Meta-analysis[publication type]

#31 (#28 NOT (#29 OR #30))

#32 Letter [publication type]

#33 Editorial [publication type]

#34 (#24 NOT (#25 OR #27 OR #31 OR #32 OR #33))

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	124
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-95
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	439-440
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	487-490
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	487-490
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	487-490
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	143-170
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	158-170

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	196-213, 282-306
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	214-221, 265-267, 308-317
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	215-218, 308-311, Online appendix
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	218-221, 316-317
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	218-221, 316-317
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	222-226, 318-324
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	269-273, 365-371
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	269-273, 365-371
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	227-240, 325-343.
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	272-275, 344-359
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	349-351
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	249-250, 360-366

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	241-250
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	342-343, 367-382
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	367-382